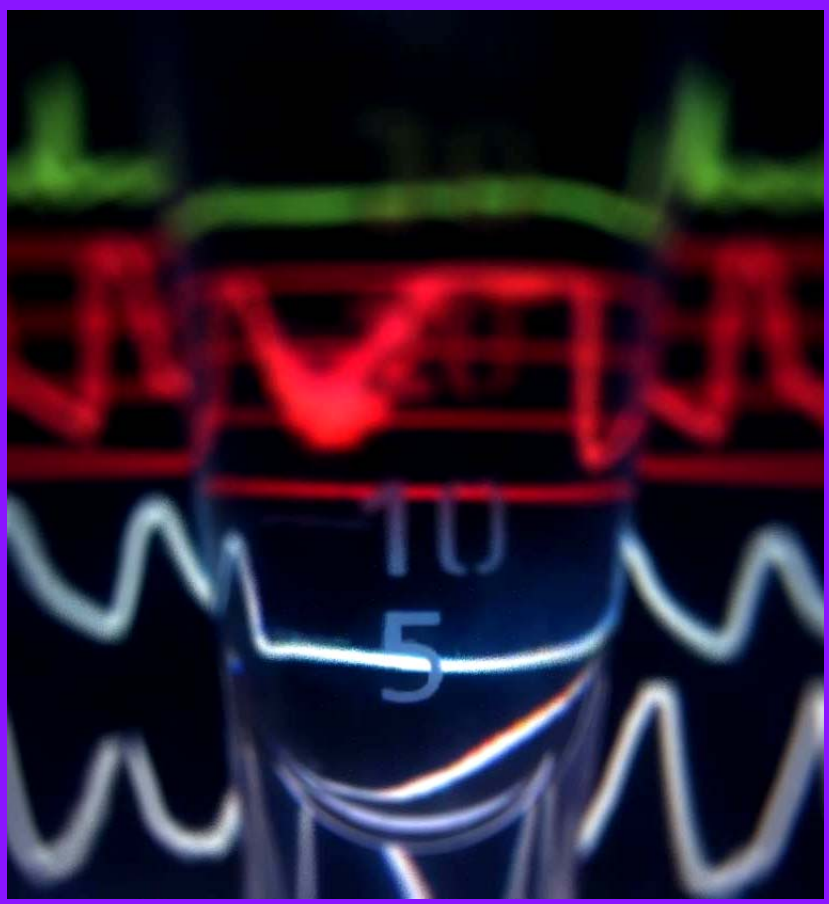
Drug Dosing in Extremes of Body Weight

in critically ill patients

1st Edition

September 2013



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Introduction to 1st edition (2013)

Obesity is becoming increasingly prevalent in the western world and consequently more common in critically ill patients. However, the dosing information for most drugs is generally obtained from studies carried out on "average weight" patients so may not be relevant to patients at the extremes of bodyweight. Yet for critically ill patients, it may be especially important to administer an optimal dose of a drug to ensure therapeutic levels are obtained.

This document which represents information and experience of dosing of drugs in critically ill patients in extremes of body weight, has been produced by the Scottish Adult Critical Care Pharmacists Network (SACCPN) in an attempt to make the necessary information more readily available.

The information provided is supported by collation of the limited literature available in this area, and by anecdotal experience of pharmacists working within critical care in Scotland. This document is intended to provide information on dosing in extremes of body weight, to allow practitioners to make informed decisions. The document does not provide a substitute for clinical judgement, and the authors trust that the information provided will only be used as part of the clinical decision making process. Every effort has been made to ensure that the information contained in this document is accurate and up to date, however no liability can be accepted for any inaccuracies or misstatements of fact contained herein, nor for any patient or clinical outcomes which may occur as a result of referring to information contained within this document. It is expected that this document will continue to evolve but as a start we have included some of the commonly used medicines used within critical care areas. It is hoped to include more monographs in future editions.

We hope that you will find the document useful and feedback is welcome. Please send any new information or experiences for inclusion in future editions to either Keith Addie (keith.addie@ggc.scot.nhs.uk) or Alan Timmins (alan.timmins@nhs.net) so that the information contained in the document can be kept up to date and relevant to clinical practice.

Many Thanks

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Background

There is little information about dosing adjustments in significantly underweight patients. There are some pieces of information in the guidance document. Some guidance may be obtained from considering dosing in children, however it is important to remember that metabolism is likely to be considerably different in children. Obesity may have no effect on morbidity and mortality in ICU[1] or may increase it[2] The latter paper provides a review of the effects of obesity on metabolism and on drug handling, as does the one by Janson and Thursky[3].

Weights used in Dosing

The following methods have been used to adjust dosing in obesity

Descriptor	Abbreviation	Formula
Total Body Weight	TBW	Weight (Wt)
Actual Body Weight	ABW	Weight (Wt)
Body Mass Index	BMI	Wt/ height $(m)^2$
Ideal Body Weight	IBW	=45.4 +[0.89 x (height {cm} – 152.4)] (+4.5 if male)
Excess Body Weight	EBW	=TBW – IBW
Maximum Body Weight	MBW	=IBW + 20%
Adjusted Body Weight	AdjBW	= IBW + [DWCF*x EBW]
Lean Body Weight	LBW	Male= [9270 x TBW] / [6680 + (216 x BMI)] Female= [9270 x TBW] / 8780 + (244 x BMI)]
Fat Free Mass	FFM	Male= [TBW x 0.285] + [12.1 x height$(m)^2$] Female= [TBW x 0.287] + [9.74 x height$(m)^2$]
Predicted Normal Weight	PNW	Male= [TBW x 1.57] – [TBW x BMI x 0.0183] – 10.5 Female= [TBW x 1.75] – [TBW x BMI x 0.0242] – 12.6
Body Surface Area	BSA	= √[(height{cm} x TBW)/ 3600]

*DWCF = Dose Weight Correction Factor (see below)

Total Body Weight (TBW) is the weight as measured. This is sometimes referred to as the Actual Body Weight (ABW), which can cause confusion with the Adjusted Body Weight (AdjBW). Body Mass Index (BMI) is rarely used for dosing, but gives an indication of the patient's stature. The Ideal Body Weight (IBW) is obtained from statistical tables relating to life expectancy, and so has little direct connection to pharmacokinetic parameters, but it is commonly used in dose adjustment. Maximum Body Weight (MBW) is a related term that is similarly approximate.

When using IBW, there is an assumption that the Excess Body Weight (EBW) has no influence on drug handling. However the adipose tissue does have some vasculature and some fluid, and in fact will usually have some influence. This can be accounted for by the Dose Weight Correction Factor. Accurate values for the factor are not easily obtained, but a value of 0.4 is often assumed. This value has been found to be useful with water-soluble drugs, particularly aminoglycosides.

Lean Body Weight (LBW), Fat Free Mass and Predicted Normal Weight take into account the gender, height and weight (e.g. tall thin people or muscular people) to estimate the fractional fat mass, so are in theory are good models for drugs that are highly hydrophilic. However they are not widely used in practice, and are more often seen in a research context with specific drugs. Body Surface Area is mainly used in cancer chemotherapy.

Much of the work relating to the above equations was carried out on previous generations, when there were fewer subjects in the upper extremities of the weight range than in the present day, and there is very little validation for the use of any of these descriptors for drug dosing. Modified weights used in altering drug doses may not be applicable for assessing ventilatory parameters, haemofiltration or nutritional requirements, and vice versa.

Pharmacology/ kinetics

Due to variable alterations in the volume of distribution, clearance and elimination half-life in obesity dosing adjustments can be complex. In obese patients, the glomerular filtration rate (GFR) may be increased relative to a "normal" patient, so in theory drug clearance may be increased. However complications of obesity, including diabetes and hypertension, may reduce clearance, so may negate this. Calculation of creatinine clearance using the Cockcroft & Gault method in obese patients should use lean body weight (or maximum body weight), since muscle mass is proportionately much less in obese patients.

An increased proportion of adipose tissue compared with lean tissue alters the volume of distribution of lipophilic drugs, TBW should generally therefore be used for dosing. For hydrophilic drugs dosing relates better to lean body mass (i.e. IBW), though as noted above there is some extra water/ blood supply to excess tissue, so an adjustment factor is sometimes added to give adjusted body weight.

As there remains a lack of good information, careful monitoring of effect and side effects is mandatory in any patients where it is suspected normal parameters may not apply.

References

1. Akinnusi ME, Pineda LA, El Sohl AA . Effect of obesity on critical care morbidity and mortality: a meta-analysis. Critical Care Medicine, 2008; 36: p151-158
2. Pieracci FM, Barie PS, Pomp A Critical care of the bariatric patient. Critical Care Medicine. 2006 ;34: p1796-1804
3. Janson B, Thursky K. Dosing of antibiotics in obesity. Current Opinions in Infectious Diseases, 25; (6) p634 - 649

Drug Dosing Information

Aciclovir

Summary of product characteristics (SPC)[1]

- Dosage in adults: 5mg/kg every 8 hours or 10mg/kg in immunocompromised patients or herpes encephalitis. [1]
- Half-life is dependent on renal function.
- Dose adjustments for renal impairment as per SPC or refer to renal drug handbook.[2]

Summary of SACCPN literature review and literature from manufacturer

Underweight patients

No data available on any dose adjustment required in low body weight

Obese patients

Literature describes acute kidney injury in obese patients where aciclovir dose was based on actual body weight.[3]

Summary/Comments

Underweight patients

No information available

Obese patients

Calculate dose using Ideal Body Weight in obese patients taking renal function into account.[2,4]

References

1. Zovirax® (Aciclovir) GlaxoSmithKline Ltd. Summary of Product Characteristics, Accessed at www.medicines.org.uk, 23rd November 2012
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe publishing, Oxford. 2009.
3. Personal communication. GlaxoSmithKline Medicines Information department. Email received 2nd January 2013
4. Antimicrobial dosing in obese patients. Clinical Infectious Diseases. 1997; 25:1;112-118.

Ambisome®

Summary of product characteristics (SPC)[1]

- Therapy is usually instituted at a daily dose of 1.0 mg/kg of body weight, and increased stepwise to 3.0 mg/kg, as required.
- No dose adjustment recommended for renal impairment.[1]

Summary of SACCPN literature review and literature from manufacturer

Underweight patients

Dose as per SPC on mg/kg basis.

Obese patients

Gilead are about to commence a pharmacokinetic study in the obese population but until data is available from this the manufacturer recommends that all patients are dosed on a mg/kg basis. Patients in the clinical studies ranged from very low birth weight neonates to adults 80kg+ but there is currently no data available from manufacturer in obese patients.[2]

There is a single case report of an obese patient with nonmeningeal cryptococcal infection successfully treated with amphotericin B plus flucytosine, followed by oral fluconazole. The dose of amphotericin was based on actual body weight; levels were not determined, the dose of flucytosine was based on IBW, and serum levels were maintained within the desired therapeutic range, without haematologic toxicity.[3,4]

Summary/Comments

Underweight patients

Dose as per SPC on a mg/kg basis.

Obese patients

Manufacturer recommends dosing on actual body weight, suggest monitoring for toxicity in obese patients.

References

1. Ambisome® (Amphotericin) Gilead Sciences Ltd. Summary of Product Characteristics. Accessed at www.medicines.org.uk 19th July 2013

2. Personal correspondence with Gilead Medical Information 11th July 2013
3. Wurtz R, Itozaku G, Rodvold K. Antimicrobial Dosing in Obese patients. *Clinical Infectious Diseases* 1997;25:112-8.
4. Gillum JG, Johnson M, Lavoie S *et al*. *Pharmacotherapy* 1995;15:251-3.

Anidulafungin

Summary of product characteristics (SPC)[1]

A single 200 mg loading dose should be administered on Day 1, followed by 100 mg daily thereafter.[1]

Summary of SACCPN literature review and literature from manufacturer

Pfizer does not recommend adjusting the dose of anidulafungin based on body weight in adult patients. Phase 3 data showed weight in anidulafungin group ranged from 35 kg to 196.5kg.[2]

Underweight patients

No specific information available.

Obese patients

Lui et al conducted a post-hoc pharmacokinetic analysis of a phase 3 study conducted in ICU patients. All patients received a 200mg loading dose on Day 1 followed by 100mg maintenance dose daily, with the exception of one 240kg patient who was given a 150mg daily maintenance dose. The higher dose was at the discretion of the principal investigator in order to ensure sufficiently high exposure to anidulafungin. The patient had global treatment success. This patient was excluded from the summary statistics.[2`]

Summary/Comments

Underweight patients

No change to manufacturer's recommended dosage

Obese patients

No change to manufacturer's recommended dosage

References

1. Ecalta® (Anidulafungin) Pfizer. Summary of Product Characteristics Accessed at www.medicines.org.uk 12th July 2013
2. Lui P et al Pharmacokinetics of anidulafungin in adult intensive care patients. *Mycoses* 54 (Suppl S2):75/121.

Benzylpenicillin

Summary of product characteristics (SPC)[1]

- 600mg to 3600mg daily, divided into 4-6 doses depending on the indication
- Higher doses as per SPC depending on indication.
- High dosage of benzylpenicllin sodium BP may result in hypernatraemia and hypokalaemia unless the sodium content is taken into account.[1]
- Dose adjustments for renal impairment as per SPC or refer to renal drug handbook.[2]

Summary of SACCPN literature review and literature from manufacturer

Underweight patients

No specific information available

Obese patients

One review recommends that for penicillins dosing should be at the higher end of the recommended treatment ranges, particularly for morbidly obese patients with more severe infections.[3]

Wurz *et al* suggested the use of a **correction formula 0.30(actual body weight-ideal body weight) + ideal body weight** where dose was increased in proportion to the excess in body weight[4].

Hites et al attempted to validate the use of the formula by carrying out a therapeutic drug monitoring study in both obese and non obese patients to evaluate the effect of obesity on attainment of therapeutic concentrations of beta lactam antibiotics[5].

In the obese population use of standard dosages of beta lactam antibiotics resulted in insufficient serum concentrations in 32% of patients and overdosed serum concentrations in 25%.

Continuous renal replacement therapy (CRRT) was identified as a risk factor for higher serum concentrations. Dosage regimens based on the **correction formula** only slightly increased serum drug concentrations but had no impact on adequacy of treatment.[5]

Roberts et al assessed therapeutic drug monitoring of beta lactam antibiotics, assessed against a target concentration of trough concentrations of 4-5x MIC, a pharmacodynamic target of 100%.[6]

74% of patient's initial doses of beta lactam doses did not achieve steady state pharmacodynamic endpoints which are believed to be associated with maximal beta lactam activity.

In 50 % of patients a dose increase was required to attain concentration targets whilst in 24% of patients a dosage decrease was required.

The aggressive pharmacodynamic targets chosen for this study appeared to have good clinical results and little observed toxicity, however lacked the statistically significant data on outcomes which could only be produced by a randomised clinical trial.[6]

No information available from manufacturer.[7]

Summary/Comments

Underweight patients

No information available

Obese patients

Dosing for penicillins, dosing should be at the upper end of the higher end of the recommended treatment ranges, particularly in morbidly obese patients with more severe infections.

Suggest dosing at upper end of range where appropriate, taking into account patient's renal function. Suggest discussing with local microbiology or infectious diseases.

References

1. Crystapen® (Benzylpenicillin) Genus Pharmaceuticals. Summary of Product Characteristics Accessed at www.medicines.org.uk 8th February 2013
2. Ashley C (Ed), Currie A (Ed), The Renal Drug Handbook. 3rd edition. Radcliffe Publishing, Oxford 2009
3. Erstad B. Dosing of medications in morbidly obese patients in the intensive care unit setting. *Intensive Care Medicine* 2004; 30:18-32.
4. Wurz R, Itokazu G, Rodvold K. Antimicrobial Dosing in Obese Patients. Clinical Infectious Diseases. *Clinical Infectious Diseases* 1997; 25: 112-8.
5. Hites M, Taccone FS, Wolff F *et al*. Case-Control study of Drug Monitoring of ß-Lactams in Obese Critically ill Patients. *Antimicrobial Agents and Chemotherapy* 2013;57(2):708
6. Roberts JA, Ulldemolins M, Roberts MS *et al*. Therapeutic drug monitoring of ß-Lactams in critically ill patients: proof of concept. *International Journal of Antimicrobial Agents* 2010;36:332-39.
7. Genus Pharmaceuticals. Personal communication with medical information department. 7th February 2013

Ceftriaxone/Cefalosporins

Summary of product characteristics Ceftriaxone (SPC)[1]

- Standard therapeutic dosage: 1g once daily
- Severe Infections: 2-4g daily, normally as a once daily dose.
- Dose adjustments for renal impairment or hepatic impairment as per SPC or refer to renal drug handbook.[2]

Summary of SACCPN literature review and literature from manufacturer[3]

Underweight patients

No information

Obese patients

Ceftriaxone

Suggest dosing at top end of licensed dose in obese patients for ceftriaxone/ cefalosporins taking into account renal and hepatic function as above. (Licensed dose of ceftriaxone in severe infections 2-4g daily).

Dose reduction/caution is necessary in patients with severe renal impairment accompanied by hepatic insufficiency.[1]

Two separate studies assessed distribution of cefalosporins given in obese male and female subjects.

Additional Information - Cefalosporins

Mann *et al* assessed subcutaneous adipose tissue concentrations of cefamandole in adult patients given as surgical prophylaxis in operations lasting greater than 3 hours. Increased doses of cefamandole (2g 3 hrly) necessary to maintain wound concentrations above MIC during surgery in morbidly obese patients.[4]

Yost *et al* assessed plasma levels after intravenous administration of cefotaxime in normal weight and morbidly obese male and female subjects. Analysis of plasma levels showed no statistical significant difference between the concentrations achieved in normal weight and morbidly obese subjects.[5]

The above studies appear to suggest that as hydrophilic drugs, standard dosing of cefalosporins will achieve adequate plasma levels however higher than normal doses may be required to achieve adequate levels in subcutaneous adipose tissue which may be relevant when they are used as surgical prophylaxis.

Summary/Comments

Underweight patients

No information

Obese patients

Suggest dosing at top end of licensed dose in obese patients for ceftriaxone/ cefalosporins taking into account renal and hepatic function as above. (Licensed dose in severe infections 2-4g daily)

Dose reduction/caution is necessary in patients with severe renal impairment accompanied by hepatic insufficiency.[1]

References

1. Rocephin®Roche. Summary of Product Characteristics Accessed at www.medicines.org.uk accessed 11th January 2013
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford. 2009.
3. Personal communication with Roche April 2013.
4. Mann HJ, Buchwald H. Cefamandole distribution in serum, adipose tissue and wound drainage in morbidly obese patients. *Drug Intelligence and Clinical Pharmacy* 1986;20:869-873.
5. Yorst RL, Derendorf H. Disposition of Cefotaxime and its Desacetyl Metabolite in Morbidly Obese Male and Female Subjects. *Therapeutic Drug Monitoring*1986;8:189-194.

Ciprofloxacin

Summary of product characteristics (SPC)[1]

- By intravenous infusion 400mg every 8-12 hours
- No advice on underweight or obese patients
- Dose adjustments for renal impairment or hepatic impairment as per SPC/renal drug handbook as relevant.[2]

Summary of SACCPN literature review and literature from manufacturer[3]

Underweight patients

No information on underweight patients however, mg/kg dosing can be used.

Obese patients

Information from manufacturer:

The manufacturer provides no specific advice. However, they provide a number of references

Allard *et al* suggest using a weight adjusted dose based on

Ideal body weight + 0.45(total body weight-IBW)

They also noted an increased total clearance in obese patients.[4]

Van Zanten *et al* suggest that higher doses of ciprofloxacin should always be used either 600mg bd or 400mg tds. Slight preference to 600mg bd as this achieves higher C_{max}/MIC ratio.[5]Hollenstein et al suggest that in obese patients, ciprofloxacin doses should be weight adjusted based on actual body weight in order to achieve the same tissue concentrations as those achieved in lean subjects although accept that this may lead to an increased risk of adverse effect.[6]

Summary/Comments

Underweight patients

No information on underweight patients however, mg/kg dosing can be used.

Obese patients

Obese patients may benefit from increased dosing and weight based doses have been suggested using IBW + (0.45 x excess body weight) and 4 – 5 mg/kg/dose. It is also suggested that 600mg bd is better than 400mg tds as this improves (C max): MIC ratio.

References

1. Ciproxin® Bayer. Summary of Product Characteristics Accessed at www.medicines.org.uk 11th January 2013
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford. 2009.
3. Personal communication with Bayer 10th January 2013.
4. Allard S *et al*. Intravenous ciprofloxacin disposition in obesity. *Clin Pharmacol Ther* 1993; 54 (4): 368-373
5. Van Zanten ARH, *et al*. Ciprofloxacin pharmacokinetics in critically ill patients: A prospective cohort study. J crit care 2008; 23, 422-430
6. Hollenstein UM *et al*. Soft tissue concentrations of ciprofloxacin in obese and lean subjects following weight-adjusted dosing. *Int J Obes* 2001;25(3):354-358

Clarithromycin

Summary of product characteristics (SPC)[1]

- By intravenous infusion 500mg every 12 hours
- No advice on underweight or obese patients

Summary of SACCPN literature review and literature from manufacturer[2]

Doses of 500mg twice daily, 1000mg twice daily and 2000mg twice daily were found to have comparable overall effect however, the higher doses resulted in increased gastrointestinal side effects.[3]

Underweight patients

No information on dosing in underweight patients.

Obese patients

No information on dosing in obese patients

Summary/Comments

Underweight patients

No information on dosing in underweight patients.

Obese patients

No information on dosing in obese patients.

References

1. Klaricid® (Clarithromycin) Abbott Healthcare ProductsP Ltd. Summary of Product Characteristics Accessed at www.medicines.org.uk 29th May 2013
2. Personal correspondence with Abbott, 29th May 2013
3. Abbott Laboratories (July 2012) Biaxin™ US Product Information, North Chicago, IL. http://www.rxabbott.com/pdf/biapi.pdf. Accessed 7th June 2013

Clindamycin

Summary of product characteristics (SPC)[1]

- Serious infections: 600mg-1.2g in two, three or four divided doses
- For more serious infections these doses may have to be increased. In life threatening situations doses as high as 4.8g daily have been used.
- Clindamycin dosage modification not usually necessary in patients with renal/hepatic insufficiency.

Summary of SACCPN literature review and literature from manufacturer

Underweight patients

No information available for dosing in underweight patients

Obese patients

Halovic *et al* demonstrated that in patients hospitalised with cellulitis and cutaneous abscess weight >100kg and BMI >40 were risk factors for treatment failure in patients treated with co-trimoxazole and clindamycin (the two most common antibiotics prescribed to patients for this indication in this study) Further subgroup analysis demonstrated that morbidly obese patients were at a higher risk of clinical failure if they were discharged on a low oral dose of clindamycin or co-trimoxazole (P=0.002).[2]

Inadequate oral doses of <10mg/kg per 24 hours in divided doses had worse outcomes in morbidly obese patients.[3]

Summary/Comments

Underweight patients

No information available in dosing in underweight patients

Obese patients

For serious /life threatening infections doses of up to 4.8g daily divided doses

Doses of <10mg/24 hours have demonstrated worse outcomes in obese patients.

References

1. Dalacin C Phosphate® (Clindamycin) Pharmacia Ltd. Summary of Product Characteristics Accessed at www.medicines.org.uk , 14th June 2013
2. Halilovic J, Heintz, Brown J. Risk factors for clinical failure in patients hospitalised with cellulitis and cutaneous abscess. *Journal of Infection* 2012;65:128-134.3
3. Janson B and Thursky K. Dosing of Antibiotics in Obesity. Current Opinion Infectious Disease 2012; 25: 634-649

Co-Trimoxazole

Summary of product characteristics (SPC)[1]

- Acute infections 960mg every 12 hours (treatment)
- *Pneumocystis Jiroveci Pneumonitis* "PCP" infections: treatment dose 20mg of trimethoprim and 100mg of sulfamethoxazole per kg of bodyweight per day in two or more divided doses.[1]
- Dose adjustments for renal impairment as per SPC or refer to renal drug handbook.[2]

Summary of SACCPN literature review and literature from manufacturer

Underweight patients

No information available on dosing in underweight patients.

Obese patients

For treatment of pneumocystis pneumonia doses of up to 20mg/kg per 24 hours trimethoprim and 100mg/kg per 24 hours sulfamethoxazole have been used.

Inadequate oral doses (<5mg/kg per 24 hours trimethoprim) had worse outcomes in morbidly obese patients.[3]

Halovic *et al* demonstrated that in patients hospitalised with cellulitis and cutaneous abscess weight >100kg and BMI >40 were risk factors for treatment failure in patients treated with co-trimoxazole and clindamycin (the two most common antibiotics prescribed to patients for this indication in this study).

Further subgroup analysis demonstrated that morbidly obese patients were at a higher risk of clinical failure if they were discharged on a low oral dose of clindamycin or co-trimoxazole (P=0.002).[4]

Summary/Comments

Underweight patients

No information available

Obese patients

As above taking renal function into account

References

1. Septrin®(Co-Trimoxazole) Aspen Global . Summary of Product Characteristics Accessed at www.medicines.org.uk, 14th June 2013
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford. 2009.
3. Janson B and Thursky K. Dosing of Antibiotics in Obesity. Current Opinion Infectious Disease 2012; 25:634-649.
4. Halilovic J, Heintz, Brown J. Risk factors for clinical failure in patients hospitalised with cellulitis and cutaneous abscess. *Journal of Infection* 2012;65:128-134.

Daptomycin

Summary of product characteristics (SPC)[1]

Indications for use	Dosage recommendation
cSSTI* **without** S. aureus bacteraemia	4 mg/kg once daily
RIE** or cSSTI **associated** with S. aureus bacteraemia	6 mg/kg once daily

* cSSTI = complicated skin and soft skin infection ** RIE = right sided infective endocarditis

- No advice on underweight or obese patients
- Dose adjustments for renal impairment or hepatic impairment as per SPC/renal drug handbook as relevant.[2]

Summary of SACCPN literature review and literature from manufacturer[3]

Underweight patients

No information beyond standard mg/kg dosing.

Obese patients

Dvorchick *et al* suggest use of total body weight for calculation of doses is appropriate based on total body weight.[3]Pai *et al* also noted that use of total body weight to calculate resulted in higher C_{max} and AUC values in morbidly obese subjects than in normal weight subjects with similar creatinine clearance values.[4]As daptomycin displays a concentration dependent pharmacodynamic effect, the authors argued that dosing based on total body weight is appropriate as dosing based on IBW may fail to reach adequate concentrations.

Summary/Comments

Underweight patients

No information beyond mg/kg dosing.

Obese patients

Appropriate to dose on total body weight ensuring appropriate monitoring for toxicity and dose adjustment for renal impairment.

References

1. Cubicin®(Daptomycin) Novartis Pharmaceutical UK Ltd. Summary of Product Characteristics Accessed at www.medicines.org.uk, 8th February 2013
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford. 2009.
3. Dvorchick BH, Damphousse D. The pharmacokinetics of Daptomycin in moderately obese, morbidly obese and matched non obese subjects. Journal of Clinical Pharmacology, 2005; 45: 48-56
4. Pai MP, Norenberg JP, Anderson T et al. Influence of morbid obesity on the single dose pharmacokinetics of daptomycin. Antimicrobial agents and chemotherapy 2007; 51(8): 2741-2747

Dexmedetomidine

Summary of product characteristics (SPC)[1]

Patients already intubated and sedated may switch to dexmedetomidine with an initial infusion rate of 0.7 micrograms/kg/h which may then be adjusted stepwise within the dose range 0.2 to 1.4 micrograms/kg/h in order to achieve the desired level of sedation, depending on the patient's response.

Summary of SACCPN literature review and literature from manufacturer

Underweight patients

As above, manufacturer recommends a lower starting infusion rate should be considered for frail patients.

Obese patients

Orion contacted. No additional information supplied from the SPC. Advise to titrate dose according to effect in all patients. Mean body mass in clinical trials = 80.6kg.

Summary/Comments

Underweight patients

Titrate dose according to response.

Obese patients

Titrate dose according to response

References

1. Dexdor®(Dexmedetomidine) Orion Pharm (UK) Ltd Summary of Product Characteristics Accessed at www.medicines.org.uk, 4th December 2012
2. Personal communication with Julie Booth, Orion Pharm (UK) Ltd 4th December 2012

Ertapenem

Summary of product characteristics (SPC)[1]

- Adults and adolescents (13-17 years of age) 1 gram(g) given once daily by the intravenous route.[1]
- Dose adjustments for renal impairment as per SPC or refer to renal drug handbook.[2]

Summary of SACCPN literature review and literature from manufacturer

Underweight patients

No information available relating to dosing of ertapenem in underweight patients.

Obese patients

Paper by Chen et al discussed pharmacokinetic and pharmacodynamics of a 1g dose of ertapenem administered to normal weight, obese and morbidly obese adults. The area under the concentration-time curve was significantly higher in normal weight subjects than in clinically obese subjects.

The authors stated that the results suggested that the standard 1g ertapenem dose may not provide adequate drug exposure in obese patients for organisms with a minimum inhibitory concentration (MIC) in excess of 0.25 to 0.5µg/ml. In Vitro studies have suggested that the following organisms may have MIC_{90}s* which exceed 0.25µg/ml: *Strep pneumoniae,* oxacillin susceptible coagulase negative staphylococci, *Acinebacter* spp and *Pseudomonas aeruginosa*.[3]

- MIC_{90S} = provide minimum inhibitory concentration in 90% of strains tested

Summary/Comments

Underweight patients

No information available

Obese patients

No dosage adjustments out with licensed dose can be recommended in either underweight or overweight patients, however the MIC90s of certain organisms should be taken into account when prescribing ertapenem.

Suggest discuss each patient with local microbiology/infectious diseases.

References

1. Invanz®(Ertapenem) Merck Sharp and Dohme Ltd Summary of Product Characteristics . Accessed at www.medicines.org.uk 5th February 2013
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford. 2009.
3. Chen M, Nafziger AN, Drusano GL. Comparative pharmacokinetics and pharmacodynamic target attainment of Ertapenem in normal-weight, obese and extremely obese adults. *Antimicrobial Agents and Chemotherapy* 2006; 50(4): 1222-1227.

Flucloxacillin

Summary of product characteristics (SPC)[1]

- Usual adult dosage 250mg to 1g four times daily (IV)
- Doses doubled where necessary
- Dose adjustments for renal impairment as per SPC or refer to renal drug handbook.[2]

Summary of SACCPN literature review and literature from manufacturer

Underweight patients

No specific information available

Obese patients

See benzylpenicllin monograph for general information on dosing of beta lactams in obesity.

Summary/Comments

Underweight patients

No information available

Obese patients

Dosing for penicillins, dosing should be at the upper end of the higher end of the recommended treatment ranges, particularly in morbidly obese patients with more severe infections.[3]

Suggest dosing at upper end of range where appropriate, taking into account patient's renal function. Suggest discussing with local microbiology or infectious diseases specialist.

References

1. Flucloxacillin Activis UK Ltd. Summary of Product Characteristics. Accessed at www.medicines.org.uk 8th February 2013
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford. 2009.
3. Erstad B. Dosing of medications in morbidly obese patients in the intensive care unit setting. *Intensive Care Medicine* 2004; 30:18-32.

Fluconazole

Summary of product characteristics (SPC)[1]

- The recommended daily doses are between 50-800mg (800mg is equivalent to 12mg/kg in a 65kg person depending on infection).
- Dose adjustments for renal impairment as per SPC or refer to renal drug handbook.[1,2]

Summary of SACCPN literature review and literature from manufacturer

Underweight patients

No specific information available

Obese patients

The only documented case is of a 185kg man, BMI 48.3, was given 1200mg and showed a lower AUC and increased fluconazole clearance. The conclusion was that the fluconazole dose should be based on the higher end of the 6 to 12mg/kg dosing range based on total body weight based on this single study.[3]

Summary/Comments

Underweight patients

No specific information available.

Obese patients

Insufficient information available to make a recommendation. See above for one case report.[4]

References

1. Diflucan®(Fluconazole) Pfizer Summary of Product Characteristics. Accessed at www.medicines.org.uk 1st August 2013
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford. 2009.
3. Chen LG., DiBaisio A., Lisco S.J., Hurford W.E. Fluconazole serum concentrations and pharmacokinetics in an obese patient. Pharmacotherapy 1997;. 17 (5 I):1023-1026.
4. Jarrett R.A, Slain D. Antifungal dosing in obesity: A review of the literature. Curr Fungal Infect rep (2011) 5:83-91.

Immunoglobulin

Summary of product characteristics (SPC)[1]

- By intravenous infusion, dose based on indication. Refer to Department of Health guidelines.[2]
- Dose adjustments for renal impairment or hepatic impairment as per SPC

Summary of SACCPN literature review and recommendations from Clinical guidelines for immunoglobulin use[2]

Underweight patients

No specific information on underweight patients however, mg/kg dosing can be used.

Obese patients

Information from guidelines:

There is limited evidence for ideal-body-weight-adjusted dosing and therefore no firm recommendation. However, a number of specialist centres and corporations from Western Australia, United States of America and the UK use the equations below: Note this is different from the equations shown on p4

Calculate ideal body weight (IBW) (kg):

IBW for males = 50 + [2.3 x (height in inches – 60)]

IBW for females = 45.5 + [2.3 x (height in inches – 60)]

Calculate dose determining weight (DDW) (kg):

DDW = IBW + 0.4 [actual body weight (kg) – IBW]

The guidelines suggest that if adjusted weight dosing for patients $\geq$30kg/m^2 or if actual weight >20% more than IBW, adjusted body weight prescribing should be considered. It is also recommended that, for adults, the dose should be rounded down to the nearest vial. Local dosing weight tables may be in use.

Summary/Comment

Underweight patients

No information on underweight patients however, mg/kg dosing can be used.

Obese patients

No strong evidence, however specialist consensus advocates the use of the DDW equation above.

References

1. Summary of product characteristics for individual normal human immunoglobulin products. Accessed at www.medicines.org.uk 27th June 2013
2. Department of Health. Clinical guidelines for immunoglobulin use. Second edition update, edited for Scotland. Department of Health. March 2013.

Levofloxacin

Summary of product characteristics (SPC)[1]

- Usual recommended dose 500mg once or twice daily depending on indication.[1]
- Dose adjustments as per SPC or refer to renal drug handbook.[2]

Summary of SACCPN literature review and literature from manufacturer

Underweight patients

No information available

Obese patients

Literature search yielded little results

Cook *et al* carried out a very small study and concluded; after a 750mg intravenous dose every 24hours, obese individuals achieve a comparable peak concentration to normal-weight individuals. However, they state obese individuals with normal renal function may clear levofloxacin more effectively and consequently have a lower AUC. No recommendations were made except to consider this variation when dosing in obese patients, particularly individuals who have a high clearance or a pathogen requiring more aggressive therapy.[3]

Luque *et al* reported on a single case of an obese individual give levofloxacin IV every 12hours. They found the AUC was doubled in this patient compared with those expected in non-obese health y volunteers.[4]

Summary/Comments

Underweight patients

No information on dosing in underweight patients.

Obese patients

Too little information to give a definitive dose recommendation in obese patients.

References

1. Tavanic®(Levofloxacin) Sanofi . Summary of Product Characteristics Accessed at www.medicines.org.uk 7th June 2013
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford. 2009.
3. Cook AM, Martin C, Adams VR and Morehead AR. Pharmacokinetics of intravenous levofloxacin administered at 750 milligrams in obese adults. *Antimicrob. Agents Chemother*. 2012, 55(7):3240
4. Luque S, Grau S, M, Colino CI & Ferrer A. Levofloxacin weight-adjsted dosing and pharmacokinetic disposition in a morbidly obese patient. *J Antimicrob Chemother* 2011;66(7):1653-4

Linezolid

Summary of product characteristics (SPC)[1]

- By intravenous infusion 600mg twice daily.[1]
- No advice on underweight or obese patients.
- Dose adjustments for renal impairment or hepatic impairment as per SPC/renal drug handbook as relevant.[2]

Summary of SACCPN literature review and literature from manufacturer

Underweight patients

There have been no studies carried out on underweight adults in any clinical trials, however in a compassionate use programme adult patients who weighed more than 40kg were treated at a dose of 600mg every 12 hours (both IV and oral). For adult patients ≤40kg a dose of 10mg/kg every 12 hours was used (both IV and oral).[4]

Obese patients

Base dose on total body weight however as body weight has an impact on linezolid clearance and absorption rate constant in patients with cystic fibrosis then for this patient group lean body weight should be used.[4]

Dosage adjustments based on BMI alone are not required and standard doses for patients with body weights up to approximately 150kg should provide AUC values similar to those seen in non obese patients.[4] 600mg twice daily was sufficient for the treatment of skin and soft tissue infections in obese adults.

Summary/Comments

Underweight patients

No studies carried out on underweight adults in any clinical trials

In a compassionate use programme of adult patients, those who weighed more than 40kg were treated at a dose of 600mg every 12 hours (both IV and oral). Adult patients ≤40kg received a dose of 10mg/kg every 12 hours (both IV and oral).

Obese patients

Dosage adjustments based on BMI alone are not required and standard doses for patients with body weights up to approximately 150kg should provide AUC values similar to those seen in non

obese patients.

600mg twice daily was sufficient for the treatment of skin and soft tissue infections in obese adults.

References

1. Zyvox® (Linezolid) Pfizer Ltd. Summary of Product Characteristics, Accessed via www.medicines.org.uk, 15th April 2013
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford.
3. 2009. Di Paolo, A., Malacarne, P., Guidotti, E., Danesi, R. and Del Tacca, M. Pharmacological Issues of Linezolid, An Updated Critical Review. Clin Pharmacokinet 2010: 49 (7); 439-447
4. Bhalodi A A, Papasavas P K , Tishier D S, Nicolau D P and Kuti J L, Pharmacokinetics of intravenous linezolid in moderately to morbidly obese adults. Antimicrobial Agents and Chemotherapy ; March 2013 57 (3), 1144-49
5. Personal Communication, Pfizer Medical Information. 15th April 2013

Meropenem

Summary of product characteristics (SPC)[1]

- By intravenous infusion 500mg-2g every 8 hours.
- No information on dosing in underweight or obese patients.
- Dose adjustments for renal impairment or hepatic impairment as per SPC/renal drug handbook as relevant.[2]

Summary of SACCPN literature review and literature from manufacturer[3]

Underweight patients

No dosing advice found.

Obese patients

See Benzylpenicillin for general information on dosing of Beta Lactams in obesity

Bearden *et al* assessed the pharmacokinetics of Meropenem administered to obese subjects.

Meropenem 1g dosed to 9 obese female patients (BMI>40). CMax 58% and AUC 66% of those reported in available literature for normal BMI subjects.

Calculated percentage of time above minimum inhibitory concentration (%T>MIC) for organisms with an MIC of 1mg/ml and 4mg/ml were 78.6% and 49.6% of an 8 hour dosing interval respectively.[4]

Due to the short half life of Meropenem, these changes had little effect on T>MIC (3%), when compared with normal weight patients. Based on the study findings the authors recommended no change in the meropenem dosing regimen for obese patients.[4]

Summary/Comments

Underweight patients

No information on dosing in these patients

Obese patients

No change recommended to standard dosing regimen.

References

1. Meronem®. (Meropenem) Astra Zeneca Summary of Product Characteristics Accessed at www.medicines.org.uk 11th January 2013
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford. 2009.
3. Personal communication with AstraZeneca November 2012.
4. Bearden DT, Earle SB, McConnell DB *et al*. Pharmacokinetics of meropenem in extreme obesity (abstract). Presented at 45th Interscience conference on Antimicrobial Agents and Chemotherapy (ICAAC); December 16-19, 2005; Washington DC, USA.

Metronidazole

Summary of product characteristics (SPC)[1]

- Usual doses range from 500mg TDS to treat established anaerobic infections (in adults) to single daily doses of up to 2g, for the treatment of trichomoniasis.
- Caution is advised in the elderly. Particularly at high doses although there is limited information available on modification of dosage.[1]

Summary of SACCPN literature review and literature from manufacturer

Underweight patients

No information found on dosing in underweight patients, although mg/kg dosing could be used.

Obese patients

An analysis of two separate studies assessing the effect of the BMI of 738 pregnant women with bacterial vaginosis (who each received a dose of 2g Metronidazole at 0 and 48 hours) on the rate of its recurrence, concluded that BMI had did not effect the rate of recurrence of and therefore it was thought that the efficacy of Metronidazole was similar among different BMI categories .[2]

Another study also noted that Pharmacokinetic parameters in pregnant patients were not significantly different from those in non-pregnant women [3]

Single doses of up to 12g have been reported to have been taken in suicide attempts/accidental overdosages with resulting symptoms limited to vomiting, ataxia and slight disorientation. [1]

Summary/Comments

Underweight patients

No specific information available, mg/kg dosing could be used.

Obese patients

Use standard dosing

References

1. Flagyl® (Metronidazole) Zentiva. Summary of Product Characteristics Accessed at www.medicines.org.uk 17th July 2013
2. Mastrobattista JM, Klebanoff MA, Carey JC, et al. The effect of body mass index on therapeutic response to bacterial vaginosis in pregnancy. Am L Perinatol 2008; 25:233-237
3. Micromedex. Metronidazole monograph. Obtained from www.micromedexsolutions.com Accessed 15th May 2013

Phenytoin

Summary of product characteristics (SPC)[1]

- Loading dose (intravenous) 10-15 mg/kg. N.B British National Formulary recommends intravenous loading dose of 20mg/kg up to a maximum dose of 2g.
- Maintenance dose 5 mg/kg daily
- No specific advice on underweight or obese patients
- Dose adjustments for renal impairment or hepatic impairment as per SPC/renal drug handbook as relevant.[3]

Summary of SACCPN literature review and literature from manufacturer[3]

Underweight patients

No specific information on underweight patients however, mg/kg dosing can be used as above.

Obese patients

Phenytoin loading dose should be calculated on the basis of IBW plus the product of 1.33 times the excess weight over IBW. Very obese individuals will require large absolute loading doses of phenytoin to rapidly achieve therapeutic drug concentrations.[5]

Summary/Comments

Underweight patients

No specific information on underweight patients however, mg/kg dosing can be used as above.

Obese patients

Obese patients may benefit from increased dosing for the loading dose using a weight of

Dosing weight = Ideal body weight + [1.33 x (Actual body weight – Ideal body weight)]

Both groups of patient will require therapeutic drug monitoring to ensure maintenance dose maintains levels within the therapeutic range. Albumin and renal function should be taken into account when interpreting the levels if total phenytoin is measured as opposed to free phenytoin levels.

References

1. Epanutin®. (Phenytoin) Pfizer Ltd. Summary of Product Characteristics Accessed at www.medicines.org.uk 26th June 2013
2. British National Formulary 65, March 2013. Published jointly by BMJ Group and Pharmaceutical Press.
3. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford. 2009.
4. Personal communication with Pfizer January 2013.
5. Abernethy DR, Greenblatt DJ. Phenytoin disposition in obesity, determination of loading dose. *Arch Neurol* 1985;42(5): 468-471.

Piperacillin/Tazobactam

Summary of product characteristics (SPC)[1]

- Usual recommended dose is 4.5g every 8 hrs.
- For severe infections and in neutropenic patients with infections the dose may be increased to 4.5g every 6 hrs.[1]
- Dose adjustments for renal impairment as per SPC or refer renal drug handbook.[2]

Summary of SACCPN literature review and literature from manufacturer

Underweight patients

No specific advice available for underweight patients.

The BNF for Children[3] lists the dose as Child 2–12 years 112.5 mg/kg (max. 4.5 g) every 8 hours for complicated intra-abdominal infections or 90mg/kg (max 4.5g) every 8 hours for other infections including in patients with neutropenia which would suggest reducing the dose in patients under 40kg or 50kg if neutropenic..

Obese patients

Suggest higher doses of piperacillin/tazobactam 4.5g 6 hrly. Maximum reported dose of piperacillin (not piperacillin/tazobactam) reported as24g/day N.B. piperacillin not licensed in the United Kingdom.[3]It has been suggested that continuous infusion for isolates with high MIC may be beneficial, however a 2013 Cochrane review found no evidence of improved outcomes when comparing continuous infusions of intravenous antibiotics to traditional intermittent infusions of antibiotics.[4,5]

Several references suggest that bone marrow related toxicity was linked to the cumulative dose of piperacillin/tazobactam and that the dose should be reduced in low body weight patients. No specific dosing advice has been found and the references all linked back to the same case report.[6]

There is currently a clinical trial running in Montpelier investigating the pharmacokinetics of Piperacillin/Tazobactam in critically ill patients over 120kg.

Summary/Comments

Underweight patients

No specific advice available, suggest mg/kg dosing as above

Obese patients

Suggest 4.5g 6hrly dependent on renal function.

References

1. Tazocin®(Piperacillin/Tazobactam) Pfizer Ltd. Summary of product characteristics Accessed at www.medicines.org.uk 12th March 2013
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford. 2009.
3. BNF for Children March 2013 accessed online 9th May 2013
4. Janson B and Thursky K, Dosing of antibiotics in obesity, Curr Opin Infect Dis. 2012 Dec;25(6):634-49 .
5. Shiu J, Wang E, Tejani AM *et al.* Continuous versus intermittent infusions of antibiotics for the treatment of severe acute infections (Review). *The Cochrane Library* 2013, issue 3. www.thecochranelibrary.com accessed 7th June 2013
6. Ruiz-Irastorza G, Barreiro G, Aguirre C, Reversible bone marrow depression by high-dose piperacillin/tazobactam British journal of haematology 95:4 1996 Dec pg 611-2
7. Pharmacokinetic of Doripenem and Piperacillin/Tazobactam in More Than 120 kg Critically Ill Patients http://clinicaltrials.gov/ct2/show/record/NCT01517815 accessed 11th April 2013.

Rifampicin

Summary of product characteristics (SPC)[1]

- Usual recommended dose 600mg -1200mg daily in 2-4 divided doses.
- A daily dose of 8mg/kg should not be exceeded in patients with impaired liver function.
- Dose adjustments for renal impairment as per SPC or refer to renal drug handbook.[2]

Summary of SACCPN literature review and literature from manufacturer[3]

Underweight patients

No information available on dosing in underweight patients.

Obese patients

Dosing based on actual body weight may lead to drug toxicity and suggest using ideal body weight. Essentially this means up to 1200mg/day in divided doses.[4]

Summary/Comments

Underweight patients

No information available

Obese patients

Dose using ideal body weight, up to 1200mg/day in divided doses.

References

1. Rifadin®(Rifmpicin) SAnofi Avensis. Summary of product characteristics Accessed at www.medicines.org.uk 8th April 2013
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford. 2009.
3. Personal communication with Sanofi-Aventis 2nd April 2013
4. Geiseler PJ et al Am Rev Respir Dis 1985; 131(6): 944-6

Sugammadex

Summary of product characteristics (SPC)[1]

- A dose of 4 mg/kg sugammadex is recommended if recovery has reached at least 1-2 post-tetanic counts (PTC) following rocuronium or vecuronium induced blockade
- A dose of 2 mg/kg sugammadex is recommended, if spontaneous recovery has occurred up to at least the reappearance of T_2 following rocuronium or vecuronium induced blockade.

Summary of SACCPN literature review and literature from manufacturer

SPC recommends using ABW for dose calculation

Underweight patients

As above

Obese patients

Van Lancker et al (1) proposed that (IBW +40%) would be appropriate for obese patients. However subsequent replies disagreed, saying that while this was true based on pharmacokinetic principles, in reality dosing based on TBW is more dependable. (2,3)

Summary/Comments

Underweight patients

Use actual body weight, as per SPC

Obese patients

Use total body weight.

References

1. Bridion®. (Sugammadex) Merck Sharp and Dohme Ltd. Summary of Product Characteristics Accessed at www.medicines.org.uk 6th September 2013.
2. Van Lancker P, Dillmans B, Bogaert T et al. Ideal versus corrected body weight for dosage of sugammadex in morbidly obese patients. Anaesthesia 2011; 66: 721 - 725
3. Carron M Freo U Parotto E and Ori C. The correct dosing for sugammadex in morbidly obese patients. Anaesthesia 2012; 67: 298 – 299
4. Sabate A and Llaurado S. Ideal versus corrected body weight for dosage of sugammadex in morbidly obese patients. Anaesthesia 2012; 67: 682

Tigecycline

Summary of product characteristics (SPC)[1]

The recommended dose for adults is an initial dose of 100 mg followed by 50 mg every 12 hours for 5 to 14 days. The duration of therapy should be guided by the severity, site of the infection, and the patient's clinical response.[1]

Summary of SACCPN literature review and literature from manufacturer

Tigecycline has not been systematically evaluated for safety or efficacy in extremes of body weight. In clinical trials, patient weight has ranged from 34kg to 200kg, and analysis of AUC and clearance did not appear to be different, suggesting there is no pharmacokinetic justification for dose adjustment based on patient weight.[2]

Underweight patients

No information

Obese patients

No information

Summary/Comments

Underweight patients

No information

Obese patients

No information

References

1. Tygacil® (Tigecycline) Pfizer Ltd. Summary of Product Characteristics Accessed at www.medicines.org.uk 12th July 2013
2. Personal Communication Pfizer Medical Information 21st January 2013

Voriconazole

Summary of product characteristics (SPC)[1]

	Intravenous	Oral	
		Patients 40kg and above	Patients less than 40kg*
Loading Dose **(first 24 hours)**	6mg/kg every 12 hours	400mg every 12 hours	200mg every 12 hours
Maintenance Dose **(after first 24 hours)**	4mg/kg twice daily	200mg twice daily	100mg twice daily

*Refers to patients aged 15 years and older.

- No advice on obese patients
- Dose adjustments for renal impairment or hepatic impairment as per SPC/renal drug handbook as relevant.[2]

Summary of SACCPN literature review and literature from manufacturer[3]

Underweight patients

Dosing as above.

Obese patients

For oral route dosing as above.

Dosing for iv weight based.

Loading dose regimen 6mg/kg every 12 hours for 24 hours then 4mg/kg every 12 hours. Phase 3 trial data was for patients 39 to 123kg actual body weight

Koselke et al performed a retrospective cohort study to evaluate voriconazole trough levels in obese BMI>35kg/m2 and normal weight BMI>18.5 – 24.9 KG/m2. Strong association between supratherapeutic concentrations in morbidly obese patients receiving 4mg/kg actual body weight.

Author suggests that for morbidly obese patients may be more appropriate to dose as ideal or adjusted body weight.

Summary/Comments

Underweight patients

Dosing as per SPC/renal drug handbook.

Obese patients

Strong association between supratherapeutic concentrations in morbidly obese patients receiving 4mg/kg actual body weight. Some evidence to support using adjusted body weight in patients with BMI >35kg/m^2 although not a definitive recommendation.[6]

References

1. Vfend® (Voricoonazole) Pfizer Ltd. Summary of Product Characteristics Accessed at www.medicines.org.uk 12th July 2013
2. Ashley C (Ed) & Currie, A (Ed). The renal drug handbook. 3rd edition. Radcliffe Publishing, Oxford. 2009.
3. Personal communication with Pfizer Medical Information July 2013
4. The pharmacokinetics and safety of intravenous voriconazole – a novel wide spectrum antifungal agent. Purkin L et al . *Br J Clin Pharmacol* 2003;56 (Suppl 1)2-9
5. Pharmacokinetics and safety of voriconazole following intravenous to oral dose escalation regimens. Purkin et al Antimicrob Agents Chemother 2002;46(8):2546-2553.
6. Koselke et al. Evaluation of the effect of obesity on voriconazole serum concentrations. J Antimicrob Chemother 2012;67:2957-2692.