Letters

Dose adjustment in renal impairment

See Papers p 263

Response from the *British National Formulary*

Editor—Vidal et al are rightly concerned that information on dose adjustment is not as well supported by evidence as our knowledge about the effectiveness of modern interventions (p 263).[1] But, as they have found, the lack of robust data to guide clinicians on the precautions to take when using drugs is woeful. Therefore, their conclusions come as no surprise to compilers of drug information.

Because there are few accessible studies on dose adjustment in renal impairment, the *British National Formulary* (*BNF*) has to rely on summaries of product characteristics, which reflect data submitted for gaining marketing authorisation. However, the *BNF* continually adjusts its position as clinically relevant information emerges; this process is summarised in appendix 2 of Vidal et al's paper.

Vidal et al's comparison of information on drugs in renal impairment was prompted by the need to populate a computerised decision support system. On the face of it, quantitative data on dose adjustment in renal impairment seem well suited for this purpose. However, a great many factors other than renal impairment influence the choice of drug and its dose. The severity of the condition being treated, the toxicity of the drug, comorbidity, and the patient's size, age, and sex can all have a bearing on the final dose chosen, but their effect is not easily quantifiable.

And even if it were possible to quantify the full effect of the clinical and demographical information, practical constraints such as the size of the available dose form sometimes make it impossible to give the calculated dose. Therefore, the most important message is often simply that renal impairment is likely to affect the dose. The clinician would still need to titrate the dose according to the patient's clinical condition or quantitative measures—for example, international normalised ratio, blood pressure, and drug concentration for drugs such as aminoglycosides and digoxin.

The *BNF* takes the view that clinicians should understand the full range of a drug's clinical properties. For example, the side effects of corticosteroids include fluid retention and readers would be expected to consider this when treating a patient with renal impairment, even though the appendix on renal impairment does not make this point. The *BNF* also provides formulation-specific information—for example, electrolyte content—which may need to be taken into account for those with renal impairment.

Categorising the degree of renal impairment often causes difficulty, and, as Vidal et al have found, there is no universal standard. The situation is further confounded by the fact that nephrologists might be interested in characterising the overall renal physiology whereas a prescriber might be interested primarily in the efficiency of drug elimination. Often, correlation between the two is poor.

Vidal et al's paper gives further impetus to the *BNF*'s plan to review its own advice on dosage adjustment in renal impairment. The review will include close scrutiny of the individual discrepancies that these authors have highlighted.

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1 Vidal L, Shavit M, Fraser A, Paul M, Leibovici L. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. *BMJ* 2005;331:263-6 (30 July.)

Response from *Martindale: the Complete Drug Reference*

Editor—Vidal et al highlight some of the difficulties that *Martindale: the Complete Drug Reference* encounters in attempting to evaluate and summarise the published literature, including the licensed prescribing information issued in different countries (p 263).[1]

The variation in the details and recommendations is partly explained by the different primary purpose and audience of the publications studied. The *British National Formulary* (*BNF*) is probably the busy UK healthcare worker's first port of call and as such reflects current licensed prescribing information and expert opinion in the United Kingdom. I imagine that the same is true for the *American Hospital Formulary System Drug Information* (*AHFS Drug Information*) in the United States. For more detail and some primary references one might consult *Martindale*, but as its coverage is international it also reflects a wider range of opinions than either of the former sources. Inevitably, it also encounters a greater variation of terminology. *Martindale* does not issue its own recommendations but reflects the published literature, and when current opinion varies this is highlighted or statements are qualified.

At *Martindale* we have long debated whether we, like the *BNF*, should define various terms, such as the degree of renal impairment, but since the original data may be differently defined it could be misleading to do so. However, when specific values are given in the literature we aim to include them. A reader of the paper by Vidal et al might be surprised by the apparent variations between sources, but they are not as great as Vidal et al would lead us to believe. The highlighted differences between *Martindale* and the *BNF* are largely minor or qualified. Some of these qualifications seem to have been ignored in the analysis.

Although Vidal et al faced a real life situation in using four common available sources, one should always consider the age of the publication being used. *Drugs Prescribing in Renal Failure* was published in 1999 but was compared with sources from 2004.[1]

We share the authors' aim that the information presented should be evidence based, but in many cases the original evidence to back up licensed prescribing information is often unpublished, poor, or absent. Even Vidal et al admit that they found few helpful papers with a Medline search. Some licensed information may contraindicate a drug in renal impairment purely because it has not been studied in this situation. In *Martindale* this would not necessarily be included as a contraindication; a potentially useful drug should not denied to any patient unless there is supporting evidence.

The authors also call for more details along the lines of those presented in the *Cochrane Library*, but this would make a quick reference source such as the *BNF* unusable, and applied logically to all facets of drug treatment would turn an already large *Martindale* into an excessively expensive multivolume tome. Detail at this level could only be included in a highly specialist publication.

Vidal et al's healthy criticism helps to ensure that we all maintain our aims of providing safe, accurate, and reliable informa-

tion. We would welcome similar examinations of other facets of drug information sources.

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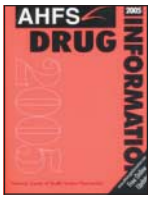
1 Vidal L, Shavit M, Fraser A, Paul M, Leibovici L. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. *BMJ* 2005;331:263-6 (30 July.)

Response from *AHFS Drug Information*

Editor—For almost 50 years *American Hospital Formulary System Drug Information (AHFS DI)* has had the most widely vetted, evidence based process for content development of any drug compendium in the US—a process that is not limited to the professional labelling (package insert) approved by the Food and Drug Administration (FDA) but includes extensive ongoing review and professional analysis of the medical literature identified through resources such as PubMed (Medline).[1 2]



Vidal et al's criticisms should have been directed principally at the inadequacies of the drug regulatory processes and pharmaceutical manufacturers in researching and publishing such information rather than at the drug information publishers (p 263).[3] In the US the FDA does not require manufacturers to conduct research establishing the impact of renal function on dosing. Instead an FDA guidance document merely provides opinion and advice and carries no regulatory force in stimulating this research.[1] Thus, whether studies should be conducted in renally impaired patients remains at the manufacturer's discretion,[4] and we can confirm that little specific primary information is currently published.

Reference material

AHFS DI is in fact fully documented.[1 5] References are not available in the print version because of space limitations, but the users' guide to *AHFS DI* clearly explains how they can be accessed.[1 5] Since 1984, reference citations have been accessible as part of the electronic versions of *AHFS DI* (www.ahfsdruginformation.com).[1 5] Currently, electronic access to 72 000 specific reference citations is available for around 480 000 statements, covering 81% of *AHFS DI* monographs. Documentation for the remainder is in the *AHFS DI* archives, from 1959.

Such access shows that the principal source of *AHFS DI* commentary on drug use for renally impaired patients originates in the manufacturers' FDA approved labelling, simply because it is often the only readily accessible source. Thus, Vidal et al's criticisms that the qualitative and undefined terms found in studied drug information sources are ill suited for practical use rightfully belong with the FDA and manufacturers, not *AHFS DI*. We cannot create such precise and specific information without adequately documented data, which are generally limited.

Roughly 30% of the total number of pertinent (systemically administered) drugs in *AHFS DI* have recommendations based *quantitatively* on specific creatinine clearances compared with the 20% reported for the subset of drugs studied by Vidal et al. We have no expeditious way of determining the number of additional drugs that would meet their second criterion for a "precise recommendation" defined by use of a term such as "avoid."

We cannot comment specifically about the discrepancies they observed among the four drug information sources studied. Generally, *AHFS DI* would defer to precautionary statements on use in renal impairment found in FDA approved labelling, which is typically more comprehensive than similar product literature in other countries. Exceptions would include a notable body of evidence from the primary literature modifying or contradicting the FDA labelled information and compelling evidence from foreign regulatory sources. Therefore, some observed discrepancies may simply reflect different international regulatory processes and conclusions.

Methodological concerns

We are concerned by Vidal et al's method of simply choosing the top 100 prescribed drugs from a single hospital over potentially more clinically relevant drugs for which both narrow therapeutic ranges and the importance of renal function in elimination have been established. Regulatory issues in the US work against clearly defining such a subset of drugs. The lack of mandated renal research and the current FDA practice of encouraging clinical trials that study *maximally tolerated* dosages in otherwise healthy adults contribute to this difficulty. As a result, there is little incentive to establish *minimally effective* dosages in renally competent adults, let alone in special populations such as those with renal, hepatic, or age related impairment.

These important factors substantially impair any attempt by publishers to establish clear dose-effect (both efficacy and toxicity) relations and make developing precise recommendations extremely difficult.

We agree that the dose and dosing interval, contraindications, and expected adverse effects should be no less evidence based than the efficacy and effectiveness of a drug. Unfortunately, few such data support this evidence based evaluation by publishers for most drugs. A focus for future change should be stimulating and publishing research on the impact of renal function on dosing.

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1 McEvoy GK, ed. *AHFS drug information 2005*. Bethesda, MD: American Society of Health-System Pharmacists, 2005.
2 McEvoy GK. Drug information resources and medication safety. In: Manasse HR Jr, Thompson KK, eds. *Medication safety: a guide for health care facilities*. Bethesda, MD: American Society of Health-System Pharmacists; 2005:253-74.
3 Vidal L, Shavit M, Fraser A, Paul M, Leibovici L. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. *BMJ* 2005;331:263-6 (30 July.)
4 US Food and Drug Administration Centers for Drug Evaluation and Research (CDER) and for Biologics Evaluation and Research (CBER). *Guidance for industry: pharmacokinetics in patients with impaired renal function—study design, data analysis, and impact on dosing and labeling*. Rockville, MD: US Department of Health and Human Services, 1998. Available at www.fda.gov/cder/guidance/index.htm
5 McEvoy GK. Obtaining references for AHFS drug information monographs. *Am J Hosp Pharm* 1987;44:1552.

Response from *Drug Prescribing in Renal Failure*

Editor—Vidal et al should be congratulated on the first scholarly, systematic review of secondary sources of prescribing information for patients with impaired renal function (p 263).[1] That they found inconsistent and conflicting recommendations across multiple sources is not surprising. Their work underscores several problems with which we have struggled to compile our dosing recommendations in *Drug Prescribing in Renal Failure*.[2]

Primary sources

Early regulatory requirements did not include formal efficacy, safety, or pharmacokinetic studies for drugs in special populations, including patients with impaired kidney or liver function. Consequently, dosing recommendations for many older drugs are based on flimsy data, including sparse case reports, common usage, and pharmacokinetic extrapolations from studies in subjects with normal renal function.

Newer drugs are studied in patients with impaired renal function, but the reports are often absent from the critically reviewed, scientific literature. The results are buried in regulatory reports or found only in other secondary sources. When multiple studies have been published, they are also frequently conflicting in their recommendations because of varied study design and analysis.

One particularly worrisome aspect is that nearly all pharmacokinetic studies are designed and funded by the drugs' manufacturers. Independent evaluations of drug dosing are rare.

Evidence for recommendations

I strongly support the contention that the process by which dosing recommendations are made should be transparent to practitioners. In the next edition of our dosing recommendations we intend to include a brief summary of the sources of information based on levels of evidence and the process by which information was obtained. For example, we will list after each drug recommendation one or more of the following or similar comments illustrating the basis for our recommendations:

- Level A: good and consistent scientific evidence

- Level B: limited or inconsistent scientific evidence
- Level C: consensus and expert opinion.

In addition to the issues found by Vidal et al, other problems related to drug prescribing recommendations continue to plague the effort to provide accurate and timely information.

New drugs and technology

Most printed compendiums of drug dosing recommendations are out of date by the time they are published. The release of new and complex molecular entities and the use of new technologies for renal replacement have made the electronic repository of drug dosing information a necessity.

We constructed an electronic data base for the revision of our drug prescribing suggestions for the authors of our book and for the use of anyone with access to the internet. Updated dosing recommendations for individual drugs can be found at www.kdp-baptist.louisville.edu/renalbook/

Individualised treatment

Even with the best evidence base, dosing recommendations for patients with decreased kidney function are extrapolated to the general population from the study of a very few patients. True individualisation of dosing cannot come from a table of dosing recommendations, but awaits new technologies for predicting drug behaviour in individual patients.[3]

Despite numerous secondary sources of drug dosing information, drug prescribing in renal failure remains imprecise and relies on interpolation, extrapolation, and estimation. The result in individual patients, at best, is guided trial and error. The work by Vidal et al illustrates Hans Christian Andersen's story *The Emperor's New Suit*: "Never the emperor's clothes were more admired. 'But he has nothing on at all,' said a little child at last."[4]

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1 Vidal L, Shavit M, Fraser A, Paul M, Leibovici L. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. *BMJ* 2005;331:263-6 (30 July.)
2 Aronoff GR, Berns JS, Brier ME, Golper TA, Morrison G, Singer I, et al, eds. *Drug prescribing in renal failure: dosing guidelines for adults.* Philadelphia: American College of Physicians, 1999.
3 Gaweda AE, Jacobs AA, Brier ME, Zurada JM. Pharmacodynamic population analysis in chronic renal failure using artificial neural networks—a comparative study. *Neural Networks* 2003;16:841-5.
4 Andersen HC. The Emperor's new suit (1837). English translation HP Paull (1872) Available at http://hca.gilead.org.il/emperor.html (accessed 20 Jul 2005).

Searching for papal scapegoats is pointless

Editor—Scalise and Bognolo ask whether the new pope will change Vatican policy on HIV.[1] On the basis of statistical evidence it would seem detrimental to the HIV situation in Africa if he did authorise such a change.

A regression analysis done on the HIV situation in Africa indicates that the greater the percentage of Catholics in any country, the lower the level of HIV. If the Catholic Church is promoting a message about HIV in those countries it seems to be working.

On the basis of data from the World Health Organization,[2] in Swaziland where 42.6% have HIV, only 5% of the population is Catholic. In Botswana, where 37% of the adult population is HIV infected, only 4% of the population is Catholic. In South Africa, 22% of the population is HIV infected, and only 6% is Catholic. In Uganda, with 43% of the population Catholic, the proportion of HIV infected adults is 4%.[2 3]

A concerted campaign, also in medical journals, has been under way after the death of John Paul II to attribute responsibility to him for the death of many Africans.[4] Such accusations must always be supported by solid data. None has been presented so far.

The causes of the HIV crisis in Africa need to be found elsewhere. The solutions must go beyond latex. If anything, the holistic approach to sexuality that Catholicism advocates, based on the evidence at hand, seems to save lives. I would welcome an editorial on that or, as a minimum, some evidence based advice on HIV.

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Competing interests: AA is a Catholic.

1 Scalise DM, Bognolo G. The new pope and medical ethics. *BMJ* 2005;330:1281. (4 June.)
2 World Health Organization. Epidemiological fact sheets. Epidemiological fact sheets. http://www.who.int/hiv/pub/epidemiology/pubfacts/en/ (accessed 24 Jun 2005).
3 Statistics by country by Catholic population. http://www.catholic-hierarchy.org/country/sc1.html (accessed 24 Jun 2005).
4 The pope's grievous errors. *Lancet* 2005;365:912.

Understanding, not wisdom, needed for capacity

Editor—Benn and Lupton describe an interesting question in comparative morality in their article on the sterilisation of young, competent, and childless adults.[1] However, by asking whether the patient has considered her present and future interests in such detail they risk minimising the safeguards enshrined in statute.[2]

The Capacity Act 2005 reiterates the words of Lord Justice Dame Butler-Sloss—that patients must show "understanding but not wisdom."[3] If the patient has understood the procedure, the alternatives, the benefits and risks of having or not having the intervention, and is expressing a voluntary choice, he or she has capacity; and patients with capacity are entitled to funded treatments.

Although efforts to ensure that patients have fully considered the issues are important, and they mention several statistics that are powerfully persuasive, it is crucial that doctors refer onwards for treatment patients they do not wish to operate on for grounds of conscience. The issue of where funding should come from is an entirely separate subject.

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1 Benn P, Lupton M. Sterilisation of young, competent, and childless adults. *BMJ* 2005;330:1323-5 (4 June.)
2 Mental Capacity Act 2005. London: Stationery Office, 2005.
3 British Medical Association. *Medical ethics today.* 2nd ed. London: BMA, 2003.

"Choose and book" does not solve any problems

Editor—In his personal view Kare-Silver describes behind the scenes at the "Choose and book" initiative.[1] Information technology does not work well when handled as a compulsory element in a political process, as the government and NHS should know.

In 1990 I could refer a patient to any specialist in the United Kingdom. What limited my use was that I did not know many specialists, most specialists provided similar services, and most patients with, for example, torn knee cartilages did not have relatives in Darlington who would like to look after them while they convalesced. But if they did, I could refer to Darlington.

Now that NHS management reads "The money will follow the patient" as "Keep the patients here to keep the money," I cannot refer distantly without a big argument.

As a corrective to this, I can refer anywhere, and hospitals that fix a knee will send a bill, always the same amount.

Years ago I suggested to our local administration that we needed two lists for the local health area—who works here and what is done here. The first would have an entry of what each person does, and the second of who does what.

I assumed that these lists would appear for Choose and book and be updated and aggregated for the remaining nation. Thus I could choose from anyone's lists, of some use perhaps once a year.

Taking the vacant slots in a specialist's future schedules and having them advertised to general practitioners would allow me to send patients who really needed an echocardiogram now to Warrington rather than Exeter, if they would travel (and thus avoid an emergency admission while waiting for it).

But Choose and book keeps commissioning staff in the loop, does not give a view of the whole NHS, and offers a choice of only five places to refer to. I am unclear whose problems it solves.

But those lists would be useful, please.

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Competing interests: AKM is active in medical information technology, particularly open source initiatives.

1 De Kare-Silver N. Choose and book—whose choice is it anyway? *BMJ* 2005;330:1093. (7 May.)