Strategy to Eliminate Pethidine Use in Hospitals

Has anybody at some stage in their career been confronted by an individual, in pain, armed with a list of manifold drug allergies, seeking pethidine? Iatrogenic dependence is one of the problems associated with pethidine and its continuing use is coming under increased scrutiny. Pethidine has been successfully removed in its entirety from our hospital and we wish to report the process, so that it can be applied to other institutions seeking to achieve a similar outcome.

The adverse effects of pethidine are well known and detailed reviews have been published elsewhere. In essence, the main problem is that pethidine provides analgesia that is no better than other opioids but has significant adverse effects. The main concerns associated with pethidine are dependence, toxicity, drug interactions and anticholinergic effects.

Although all opioids are capable of causing dependence, pethidine's potential for abuse is higher than other opioids, which may be related to the greater degree of euphoria that is often reported.[1-4] Although pethidine has a short duration of action, it produces even at therapeutic doses the active metabolite, norpethidine.[5] Norpethidine's main toxicity is due to its capacity to enhance serotonin levels, which is increased when the duration of pethidine use is prolonged, the dosage is high or there is concomitant renal impairment or hepatic enzyme induction.[6,7] These conditions are likely to occur in patients receiving pethidine by patient-controlled analgesia. Pethidine delivered by such devices is associated with a high incidence of serious adverse effects.[8-10] Norpethidine is also responsible for a wide range of drug interactions, the most serious resulting from precipitation of the serotonin syndrome, that can occur with concomitant use of pethidine with monoamine oxidase inhibitors, tricyclic antidepressants and tramadol.[11-13] Pethidine use restricts the range of drugs that can be used concomitantly.

Pethidine was originally synthesised for its anticholinergic properties and can produce tachycardia, xerostomia and attenuation of accommodation, as well as central nervous system effects such as confusion and disorientation.[4] If these effects are well documented and alternatives are available, why is pethidine still being used? The answer, in part, lies in its history. Following its synthesis in 1939, pethidine was released for clinical use eight years later. At that time, the only other opioid available was morphine, whose spectrum of adverse effects was well known, and the hope was that somehow this new opioid would offer substantial advantages over morphine, and perhaps even replace it.

As outlined in the recent review of pethidine's pharmacology by Latta, this initial enthusiasm for pethidine was fuelled by early studies that purported to demonstrate that compared to morphine, pethidine possessed superior analgesia, had less adverse effects and possessed a beneficial effect on relaxation of smooth muscle.[15] Despite the fact that most of these claims were refuted almost as quickly as they appeared, for example papers showing a lack of smooth muscle relaxing effect appeared in 1947, the dye was cast, and the myths surrounding the enhanced clinical efficacy of pethidine have persisted into the 21st century.

Prescribing of pethidine is discouraged in many countries. In Australia, its prescription in the community setting has been restricted by the Pharmaceutical Benefits Advisory Committee and pethidine was removed from the Emergency Drug (Doctors' Bag) supplies in 2005. There is a considerable groundswell movement that is questioning the ongoing use of pethidine in all practice settings. In the US where pethidine usage has always been substantial, its continued use, especially in postoperative pain management has been questioned.[3,16-18]

In hospitals, an enterprising start has been made by reducing or eliminating pethidine use in emergency departments.[19] The result has been positive with emergency physicians having no difficulty in using other drugs for pain management and at the same time reducing the time spent dealing with pethidine-seeking individuals.

The time has come to eliminate pethidine from the rest of the hospital. How can this be accomplished? We report the process by which pethidine was removed in its entirety from the Royal North Shore Hospital – within 12 months and with a minimum of tears. A clear plan of attack is needed to optimise the chance of success.

The first step is to gather key scientific papers that debunk the pethidine myths. The difficulty in this area is not finding the papers – the literature is replete – but rather to select papers that give accurate and thorough overviews of the topic. Shipton's work is an excellent example of scientific clarity, as the author points out in half a dozen pages the problems associated with pethidine use and the reasons why it should not be used.[20] The critical review by Latta et al. and the position statement on pethidine use prepared by the NSW Therapeutic Assessment Group are also highly recommended.[15,21]

The second step is to enlist the hospital drug and therapeutics committee to take the lead. The process will not succeed without strong support from this quarter and also needs leadership from senior doctors, pharmacists and nurses.

The third step is to identify areas of pethidine use within the hospital. Areas such as obstetrics, gastroenterology and endoscopy will probably represent the main usage. Pethidine has a long tradition of use in obstetrics based on the myth that it does not cause respiratory depression and has no effect on the fetus.[15] Studies have shown that the effects on the fetus are significant and can last for six weeks after delivery.[22] If more evidence is needed, the study by Olaffsen et al. should be considered, as it demonstrated that pethidine and other opioids do not provide any significant analgesia in labour and simply sedate the patient![23] Furthermore, patients given pethidine have a significant incidence of adverse effects such as nausea, vomiting and dizziness.[24] With regard to its use in gastroenterology, prescribers may find the truth unpalatable. The sphincter of Oddi is sensitive to all opioids at equianalgesic doses and pethidine is no more effective in the management of biliary colic than any other opioid, or non-steroidal anti-inflammatory drug for that matter![25,26]

Historically, pethidine has also been the drug of choice in the management of shivering associated with conditions, such as recovery from general anaesthesia following spinal or epidural analgesia or as a result of blood transfusion or chemotherapy. However, recent reports have shown that this is not a response unique to pethidine and that all opioids possess the capacity to suppress shivering.[27,28] Furthermore, a number of non-opioid analgesics, such as tramadol and ketamine have shown to be effective or superior in the management of shivering.[29,30] It is important to recognise this use for pethidine, as pockets of usage will be found in areas such as general and cardiothoracic intensive care, haematology/oncology and post-anaesthesia.

There can be no success in eliminating pethidine from the hospital unless alternatives can be offered. What will prescribers use instead of pethidine? The most obvious option is to use morphine. One reason often cited for avoiding morphine is that a large cohort of patients claim to have a preexisting morphine 'allergy'. Many patients claim to have experienced nausea, vomiting, sedation and mild pruritus following morphine use.

These do not constitute an 'allergy' but rather adverse effects that constitute a class effect of the opioids. However, once morphine is listed as a drug to which the patient is allergic, it makes its prescription problematic, as most doctors tend to respect patients self-reported drug allergies.[31] The next option is to consider the use of non-opioid analgesics. Non-steroidal anti-inflammatory drugs are potent analgesics and are available in parenteral formulations (e.g. parecoxib). Non-steroidal anti-inflammatory drugs have their own concerns but provided simple guidelines are followed and prescribing is restricted to 48 hours, the risk of serious adverse events is considerably reduced.

The final option is that even if drug choices are limited by pre-existing 'allergies' there are a number of opioid alternatives of the phenylpiperidine group. Fentanyl, hydromorphone and oxycodone are suitable alternatives to pethidine or morphine and are available in parental formulations. Diamorphine is also an option in countries where it is available. Although prescribers may be less familiar with some of these drugs, they provide the same degree of analgesia as other full opioid agonists.

The evidence against the continuing use of pethidine is compelling and other authors have detailed their strategies to restrict or limit its use.[16-18] At the Royal North Shore Hospital, following the step-wise process outlined, pethidine has been removed from the formulary for almost a year. Prescribers have found alternative analgesics and there have been no complaints. Hopefully, the steps outlined can be successfully implemented in other institutions.

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Whither 'Rational' Use of Drugs?

Logic ... the dance of those impotent to create.'[1]

Does anyone think that, by a minute refinement of logic, he has demonstrated the truth and established the correctness of … opinions? Logic imprisoned by the senses is an organic disease.'[1]

Is medicine an art or a science? This is a question regularly posed in undergraduate pharmacy courses. The customary answer that a student might expect to hear is that it is really a bit of both. However, for centuries, apologists for Western medicine have strongly asserted that deductive logic and sound science are the sole basis for good medical practice. Where then is art and creativity within such a framework? How is it possible to mix these two fundamental human activities in one harmonious integrated whole?

Of course, the *Journal of the American Medical Association* still publishes on its stately front cover, tasteful (if somewhat prosaic) representations of nice pieces of fine art. However, it seems unlikely that keeping such icons front and centre in key medical publications is the full extent to which art can be found in the world of medicine.

Contemporary pharmacy practitioners conventionally rely on evidence about pharmaceuticals to frame therapeutic options for patients and physician colleagues. Indeed, in institutional practice we regularly go to extraordinary lengths to sift the literature for the best evidence and the best science, so that we can deduce wise options for a specific therapeutic problem. It is certainly not easy to see the art in this form of activity.

However, if art actually plays a part in medicine, pharmacy practice framed in this way seems a long way from it.

In hospital pharmacy practice, we too often busy ourselves with building and policing formulary systems for pharmaceuticals in our institutions. This seems to be perhaps the very least art-infused activity in which any person could become involved as we try to support good medical practice. Our intentions in such coercive systems are of course superficially good – we are hoping to support medical learning, save money for our institutions, and by restricting available choices, to make therapeutic decisions perhaps more logical.

The idea of rational drug therapy has gained a great deal of currency over the past 20 years. A quick search of the World Health Organization's web site for the words 'rational drug use' reveals 6340 postings. Even the World Bank when it interests itself in health systems development portentously announces rational drug use as integrating two principles – use of drugs according to scientific data on efficacy, safety and compliance and cost-effective use of drugs within the constraints of a given health system. It is clear that Australian hospital pharmacy practice is in good company when it promotes 'rational' drug use!

However, great caution is needed when we consider the extent and limits of rationality that can be applied to therapeutic decision-making. Professor Jack Dowie, a commentator with impeccable credentials as a logician wisely points out that while certain aspects of therapeutic decision making can be subjected to deductive logic, 'irreducible uncertainty' in health and disease make it impossible to accurately predict exactly what will be a correct therapeutic decision and what, an incorrect one.[2]

Professor Dowie separates diagnostic decisions from patient management decisions, and points out that while the former may be prove in the long run to be either correct or incorrect, patient management decisions have entirely different qualities. Management decisions such as which drug to prescribe are of necessity based on value judgments interlacing rational thinking. Our rational thought in the healthcare context is of course underpinned by evidence-based medicine and all we hold dear about science in healthcare. (Of course the recent reminders of corruption of health sciences' underlying 'evidence' a couple of months ago is particularly discomforting.)[3,4]

Professor Dowie points out that as far as intuition and value judgments are concerned it is impossible to create 'gold' or 'correct' standards: in therapeutics, value judgments are an inescapable element of human decision-making in conditions of uncertainty. As a consequence, he concludes that only at the very moment of primary decision-making could one conceivably evaluate the actual quality of a patient management decision. Impossibly in such a situation, he points out that one would also need to be able to apply sets of values which were both externally and internally consistent; that is externally consistent between different people and institutions, and internally consistent for the same individual or entity across time and in differing circumstances.

Additionally, and perhaps even more disturbingly, Professor Dowie goes so far as to suggest that judging rectitude of management (or therapeutic) decisions some time after they have been made is probably indefensible. For hospital pharmacists, the implications of this idea are profound indeed. If the basis for drug utilisation review is thus questioned we need to give serious thought to the way we go about this particular commonly performed professional activity.

These contentions lead to uncomfortable conclusions about the way pharmacists carry out their central role of providing support for other health professionals in their judicious selection of pharmacotherapies.

It is perhaps time for pharmacists engaged in enforcing drug availability policies in institutions to review the literature again about clinical decision-making. In light of these considerations it may be timely for us to re-evaluate the ethical basis for our current approaches, and to perhaps make adjustments as a result of our findings.

A failure to acknowledge and accept value judgments at the point of prescribing decision-making, and hasty assessments of prescriber rectitude or fault in therapeutic decisions (when viewed in retrospect) can be seen as failures of the pharmacy profession to understand the meaning of art in medicine.

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Keeping up with the Evidence, Trials and Journals

In recent months, as always, the literature has carried important new information for practitioners. The challenges are to read, 'digest' and apply new information in a timely manner. Sometimes, reports are difficult to interpret and may even provide apparent contradictions. Most of the time, there seems to be simply too much information. Nonetheless, what distinguishes a competent practitioner is the ability to seek, interpret and apply new knowledge on an ongoing basis. This is no small task. Two recent issues highlight this aspect of practice.

In June the *New England Journal of Medicine* published a paper that illuminated the mechanisms of heparin contamination and the adverse clinical consequences.[1] Every hospital pharmacy dealt with the practical issues in response to these reports earlier this year—product recalls and endeavouring to answer queries on the status and safety of the drug. The editorial in the *New England Journal of Medicine* described the events that lead to a rapid assessment of the scientific basis for the reported hypotensive events, the international responses and the potential for ensuring the future global supply chain.[2]

Also in recent weeks, two important trials that contribute to the evidence on management of diabetes have been reported. Interestingly, there are apparent key differences between the studies, which means that the translation of trial evidence into practice guidelines needs careful consideration. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trials have both been reported in the *New England Journal of Medicine*.[3,4] Both studies were conducted in patients with type 2 diabetes and both studies involved intensive lowering of blood glucose. Although there were similar clinical issues involved, the studies focused on different endpoints and an interpretation of the studies could be that different results have been obtained. So, what should be the target HbA_1C? Is this a straightforward question? In a commentary, Krumholz reminds us that this is in fact a complex question and surrogate endpoints are but one measure of patient outcomes.[5] In the editorial by Cefalu, we are reminded that the answer to the questions about cardiovascular disease and glycaemic control remain unanswered, and more trials will be needed.[6]

Although never ending, the task of critically assessing the literature and incorporating up-to-date evidence into practice is critical. Pharmacists must undertake to be expert at interpreting clinical trial results and be thoughtful about application of evidence into practice. Although not easy, this remains one of the most interesting and challenging aspects of practice.

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