

## SPECIAL ARTICLE

# Administration of drugs outside of Product Licence: awareness and current practice

Audience responses from the 1997 Annual Meeting of the Obstetric Anaesthetists' Association

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**SUMMARY.** An interactive audience response system was used to collect information from members of the Obstetric Anaesthetists' Association at the 1997 Annual Meeting about the drug use that is unsupported by the Product Licence. The responses confirm that both licensed and unlicensed drugs are widely used in clinical practice outside the limitations imposed by Product Licence. The commonest types of unlicensed administration in obstetric anaesthetic practice are the use of mixtures and epidural or spinal administration of opioids. Despite widespread awareness of the subject, there appears to be considerable ignorance about the indications for which many commonly used drugs are licensed, even amongst a specialist audience. A majority of audience members expressed a view that the OAA should play a pro-active role, either by polling members about their current practice, or by issuing guidelines on reasonable drug practice in obstetric anaesthesia, or both. Potential implications of these are discussed.

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## INTRODUCTION

Drug availability is controlled in the UK by the Medicines Control Agency under the 1968 Medicines Act,<sup>1</sup> and the vast majority of drugs administered by anaesthetists have been issued with a Product Licence. This provides specific information about the indications, contraindications, dosage and routes of administration for a drug, as well as stipulating other criteria, such as the nature of the drug, its pharmaceutical form, strength and packaging. Details of the Product Licence for branded drugs (e.g. Marcaine® – Astra) are reproduced in the drug data sheet or summary of product characteristics (SPC) to be found in the Association of the British Pharmaceutical Industry (ABPI) Compendium.<sup>2</sup> Information about all drugs

with Product Licences, including generic products such as bupivacaine from other manufacturers, is published monthly in a governmental document, The London Gazette (The Edinburgh Gazette in Scotland, or the Belfast Gazette in Northern Ireland).<sup>3</sup>

The Food and Drugs Administration (FDA) in the USA fulfills a similar role to the Medicines Control Agency in the UK. Within the European Union, drugs may be licensed either nationally or through the European Agency for the Evaluation of Medicinal Products (EMEA) which will license drugs for pan-European use. Product Licence details vary frequently from country to country: for instance, Calciparin (Sanofi Winthrop – heparin calcium) is licensed for the treatment of disseminated intravascular coagulation in Australia but not in Europe or the USA.<sup>4</sup> Limited details about the varying international licensed indications for use may be found in Martindale – The Extra Pharmacopoeia.<sup>4</sup>

A few drugs have no Product Licence, and fall into one of two categories in the UK. Unlicensed Specials (such as i.v. magnesium sulphate) are made by manufacturers (or sometimes hospital pharmacies) that hold a licence to manufacture a product according to specific instructions from clinicians. So-called Prepared Medicines such as total parenteral nutrition

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are most frequently made up in hospital pharmacies for specific named-patients, and are only for use in the same hospital or Trust.

The 1968 Medicines Act allows registered medical practitioners clinical freedom to prescribe drugs for uses other than those defined in the Product Licence. Any drug used in a way not specified in the Product Licence, or a Special or a Prepared Medicine is unlicensed. Similarly, the Food and Drugs Administration (FDA) in the USA allows 'off-label' administration of drugs, and recognizes that 'off-label' use by prescribers is often appropriate and may represent the standard of practice. However, responsibility (and hence liability) for any adverse reaction occurring when a drug is administered in this way is wholly that of the doctor (and probably his/her employers), unless there is a question of product quality. As a consequence, risk management teams and employing trusts are taking a growing interest in unlicensed drug administration, and may begin to challenge it. Relatively few drugs are licensed for use in pregnancy, hence obstetrics and obstetric anaesthesia are areas of medicine in which many, perhaps the majority, of unlicensed drug uses occur. Paediatrics is an area similarly affected. This has obvious potential implications for both practitioners and hospital management.

The availability of an interactive audience response system at the 1997 Annual Meeting of the Obstetric Anaesthetists' Association (OAA), provided an opportunity to explore the knowledge, current practice and opinions of obstetric anaesthetists about drug licensing. The results are presented below.

## METHODS

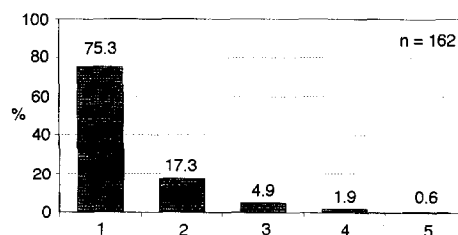
A computer assisted interactive audience response system (Brähler ICS UK Ltd) was used at the 1997 Annual Meeting of the OAA in Guildford, Surrey. One of the sessions included a presentation on the use of drugs outside of Product Licence by one of the authors (PRH). The Brähler system allowed audience members to make one selection from up to 10 options anonymously, and was used to collect and display responses to questions raised by the speaker during this presentation. A maximum of 169 audience members registered responses to questions.

## RESULTS AND EXPLANATION

Quotations in italics are taken from the 1997–98 ABPI Compendium of datasheets and summaries of product characteristics,<sup>2</sup> and the number of OAA members responding is shown on the respective figures. Where appropriate, the correct answer is shown in bold.

### Q1. In your regular anaesthetic practice how often do you think you administer drugs outside of their Product Licence?

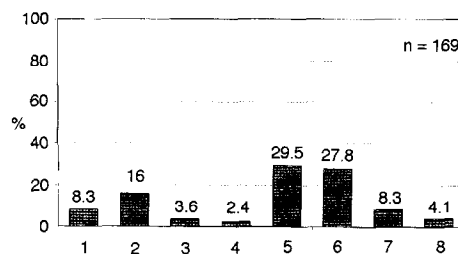
1. Frequently
2. Occasionally
3. Rarely
4. Never
5. Don't know



The vast majority of the audience were aware of the widespread unlicensed use of drugs.

### Q2. Which of the following are licensed for use in obstetrics?

1. Intravenous propofol 200 mg for cervical cerclage in 2nd trimester of pregnancy
2. Intramuscular hydralazine 10 mg in pre-eclampsia
3. Sub-lingual nifedipine 10 mg in pre-eclampsia
4. Intravenous nitroglycerine 50–100 µg for retained placenta
5. **Epidural Marcaine ® 0.5% + 1:200,000 adrenaline (pre-packed) for labour analgesia**
6. None of the above
7. All of the above
8. Don't know



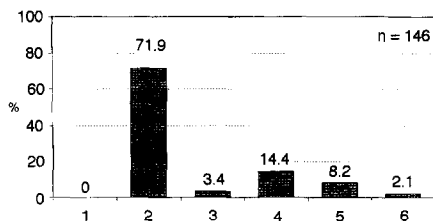
Propofol is not licensed for use at any stage in pregnancy, and unlike many other drugs whose data sheets are less specific, the entry under propofol states '*propofol should not be used in pregnancy ... should not be used for obstetric anaesthesia*'. Intramuscular hydralazine has been used for many years in the management of pre-eclamptic hypertension, but is, in fact, only licensed for use by the intravenous route. Nifedipine is licensed for the treatment of all grades of hypertension, but not in pregnancy and only by the oral route. Recent concerns about the unpredictable, sometimes catastrophic, effects of sublingual nifedipine capsules suggest that this may become a litigious minefield.<sup>5</sup>

Several case reports have suggested that small intravenous (or inhaled) doses of nitroglycerine may safely produce uterine relaxation and allow placental removal without recourse to anaesthesia.<sup>6-9</sup> However, this new and interesting use of nitroglycerine has not been supported by any changes to the Product Licence.

Pre-packed Marcaine® (bupivacaine) 0.5% with adrenaline is licensed for epidural use in labour, although the dense motor block that is likely to be produced by this solution makes it unsuitable for routine labour analgesia. Very few obstetric anaesthetists are likely to use this solution in labour, and hence changing clinical practice has left a drug licensed for a clinically inappropriate indication.

**Q3. Which of the following are licensed for use for caesarean section?**

1. Intravenous propofol 200 mg (maximum)
2. Intravenous thiopentone 300 mg
3. Intravenous ketamine  
1 mg/kg supplementation of epidural
4. None of the above
5. All of the above
6. Don't know

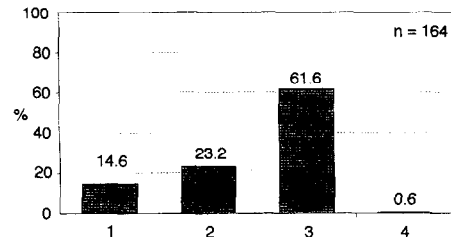


Thiopentone is licensed for use in pregnancy, but only up to a maximum dose of 250 mg. In addition, specific mention is made of the technique of administration: '*Fractional administration is advised rather than single-dose method. For induction inject 4–6 ml of solution in 10–15 seconds ... then pause for 30 seconds to 1 minute to observe the effect of the drug ... a further quantity of the solution may then be given if indicated*'. Obviously, if adhered to, the dose limitation would put women at significant risk of awareness, and the technique described is incompatible with the current standard technique, the rapid sequence induction. Clearly, the Product Licence has not been amended as clinical practice has evolved, and is completely inappropriate for contemporary clinical use.

Ketamine is licensed as a supplement to anaesthetic agents, and is '*clinically compatible with commonly used general and local anaesthetic agents*'. Pregnancy is not specifically mentioned, and the dose recommendation '*is in the same range*' as for other uses (i.e. 1–4.5 mg/kg for induction). However, doses of this order as supplementation for a sub-optimal regional technique are excessive, and inappropriate for clinical use.

**Q4. Have you used propofol in pregnancy in the past year?**

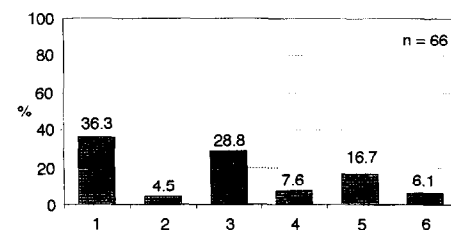
1. Yes – often
2. Yes – occasionally
3. No
4. Don't know



Almost 40% of the audience admitted that they had, either frequently or occasionally, used propofol in pregnancy. Despite the paucity of evidence to suggest that propofol is unsafe in pregnancy, the data sheet strictly prohibits its use, and by issuing unequivocal instructions the manufacturers effectively limit liability for any adverse fetal outcome.

**Q5. If you have used propofol in pregnancy in the past year, what was it usually for?**

1. Cervical cerclage
2. Caesarean section
3. Incidental surgery during pregnancy
4. Other indications
5. Several indications
6. Don't know

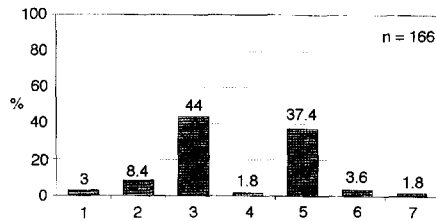


Of the 66 anaesthetists who admitted to having used propofol in pregnancy, the commonest indication was for cervical cerclage, followed by incidental surgery in pregnancy and other multiple indications. Only three anaesthetists declared they had used propofol for induction at caesarean section.

**Q6. Which of the following are licensed for use for caesarean section?**

1. Epidural 20 ml bupivacaine 0.5% + fentanyl 50 µg
2. Epidural 20 ml bupivacaine 0.5% + 0.1 ml NaHCO<sub>3</sub>
3. Spinal bupivacaine 0.5% plain
4. Spinal bupivacaine 0.5% hyperbaric + fentanyl 10 µg

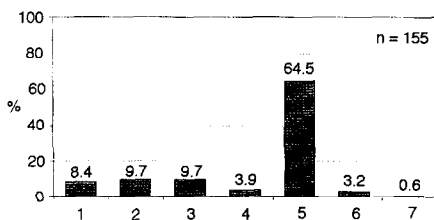
5. None of the above
6. All of the above
7. Don't know



The addition of opioids (fentanyl) to bupivacaine forms an unlicensed mixture, and opioids are also not licensed for epidural or intrathecal use. Similarly, despite published evidence of the clinical value of alkalisation with sodium bicarbonate solution, this is an unlicensed mixture to use via any route. Bupivacaine 0.5% is the main agent used for spinal anaesthesia in the United Kingdom, but only the hyperbaric preparation is licensed for this purpose.

**Q7. Which of the following are licensed for analgesia following caesarean section?**

1. Intravenous PCA Morphine 50 mg + droperidol 7.5 mg in 50 ml
2. Rectal diclofenac 100 mg twice daily
3. Epidural diamorphine 2.5 mg as a single dose
4. Epidural PCA bupivacaine 0.1% solution + fentanyl 2 µg/ml
5. None of the above
6. All of the above
7. Don't know



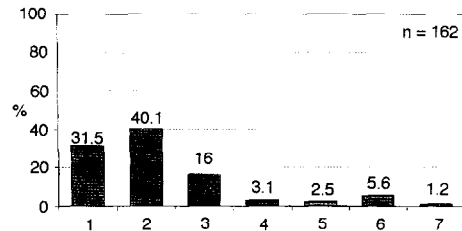
The addition of droperidol to morphine produces an unlicensed mixture. Even without droperidol, however, a morphine solution may not be licensed for use in a PCA device unless specifically marketed as such (usually only pre-packed commercially prepared syringes, e.g. Rapiject® 50 ml syringes).

Diclofenac is licensed for a maximum divided daily dose of 150 mg. Twice daily rectal administration is currently popular, but the lack of 75 mg suppositories makes this slightly inconvenient.

**Q8. When there are no obvious contraindications, how do you usually prescribe NSAIDs following caesarean section?**

1. Diclofenac 150 mg daily (maximum) in regular doses

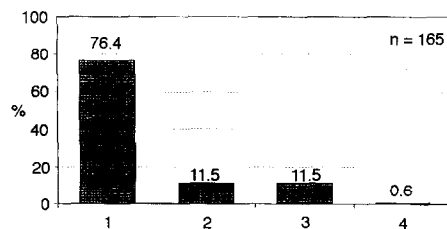
2. Diclofenac 150 mg daily (maximum) in p.r.n. doses
3. Diclofenac 100 mg twice daily
4. Usually prescribe another NSAID
5. Don't usually prescribe NSAIDs
6. Other
7. Don't know



Over 70% of the audience use 150 mg as the maximum daily dose of diclofenac, although another 16% regularly gave 200 mg daily. Very few members (2.5%) did not prescribe NSAIDs following caesarean section, and almost half prescribed it in regular doses, as opposed to p.r.n.

**Q9. Do you commonly use a bupivacaine solution with added fentanyl for epidural use for labour analgesia?**

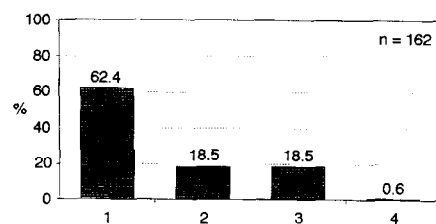
1. Yes – often
2. Yes – occasionally
3. No
4. Don't know



Over 88% of the audience used an (unlicensed) epidural bupivacaine + fentanyl solution for labour analgesia, most of whom used it often.

**Q10. Do you commonly add fentanyl to the local anaesthetic solution for epidural use at caesarean section?**

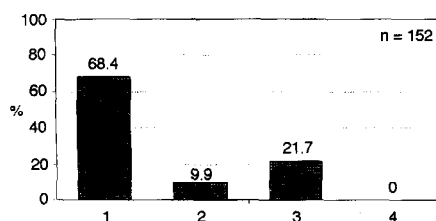
1. Yes – often
2. Yes – occasionally
3. No
4. Don't know



Again, over 80% of the audience used epidural fentanyl to supplement bupivacaine epidural anaesthesia for caesarean section, most of whom used it often.

**Q11. Do you commonly add opioid to bupivacaine for intrathecal use at caesarean section?**

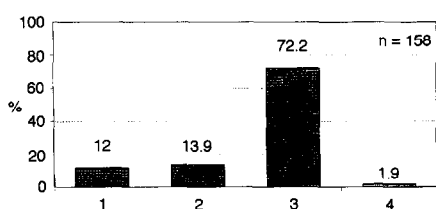
1. Yes – often
2. Yes – occasionally
3. No
4. Don't know



Two-thirds of the audience admitted to giving an intrathecal opioid frequently at spinal anaesthesia, presumably using fentanyl and/or diamorphine or morphine.

**Q12. Have you been challenged by your Hospital Trust, Drugs Committee or Pharmacy about the unlicensed administration of drugs?**

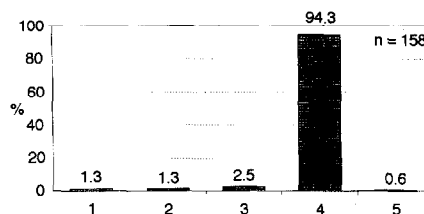
1. Yes – for information gathering only
2. Yes – with pressure to justify or stop unlicensed use of drugs
3. No
4. Don't know



Approximately a quarter of the audience had been approached by some body within the hospital to discuss the unlicensed use of drugs, and in over half these cases (13.9% overall) some pressure to modify or justify drug practice was experienced.

**Q13. Have you been involved in litigation as a defendant in a case where the unlicensed administration of drugs has been a significant issue?**

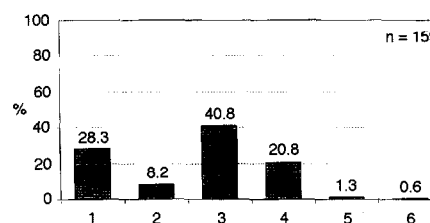
1. Yes
2. Yes – unlicensed use successfully defended
3. Yes – unlicensed use criticised
4. No
5. Don't know



Eight members of the audience reported having been defendants in a legal case where unlicensed drug administration was a central issue. Two of these members reported that the practice had been successfully defended, although in four others, unlicensed drug administration had been criticised, possibly with financial consequences.

**Q14. Do you think there is a role for the OAA to play as a 'responsible body of opinion' and that it should:**

1. Poll current practice of OAA members for publication
2. Issue guidelines on 'reasonable drug practice in obstetric anaesthesia'
3. Both of the above
4. Neither of the above
5. Other options
6. Don't know



Almost 80% of the audience expressed an opinion that the OAA should take a pro-active role in this subject, and either poll members for information about their current practice, or issue OAA guidelines on reasonable drug practice, or both. Only 20% of the audience felt that the OAA should do neither of these. Some of the potential implications of this involvement by the OAA are discussed below.

## DISCUSSION

Two-thirds of the audience at the OAA meeting comprised consultant anaesthetists or equivalent (personal communication – OAA Secretariat), and all may be assumed to have an interest in the speciality of obstetric anaesthesia. Whilst the reliability of audience responses using an anonymous electronic system may be questioned, the authors do not consider there to be significant reason to challenge the results recorded. However, the audience was asked to make

rapid responses to questions, and it is possible that, had more time been available for reflection, some of the more contentious questions (e.g. Q14) might have been answered differently.

The collated responses from the audience raise several issues and highlight both the complexity and the difficulties inherent in the drug licensing system. Almost all of the (educated, super-specialist) audience were aware that they used drugs in an unlicensed manner in their own anaesthetic practice (Q1). In particular, there was general awareness that most mixtures of drugs were unlicensed, and that opioids were not licensed for epidural or spinal use (Q7). Despite this, however, a very high proportion admitted to using opioids in combination with local anaesthetic drugs for labour analgesia or caesarean section (Q9, Q10, and Q11). This is consistent with similar survey findings from North American obstetric anesthesiologists questioned at the 29th Annual Meeting of the Society for Obstetric Anesthesia and Perinatology (SOAP) in 1997.<sup>10,11</sup> The vast majority of obstetric anaesthetists in the UK and North America use unlicensed spinal opioids apparently frequently and knowingly. Much clinical research in obstetric anaesthetic practice, particularly regional anaesthesia, has demonstrated the beneficial effects of drug combinations (such as the addition of opioids, NaHCO<sub>3</sub>, epinephrine, clonidine etc to local anaesthetics, mixtures of local anaesthetics) and many have entered routine clinical practice. Few are licensed.

However, outside of these areas (mixtures and opioids) there was considerable confusion over the licensing of a number of commonly used drugs. This undoubtedly results from the complexity of the subject, and the wide range of drugs in current use. Small changes to dosage, preparation or administration may unwittingly move a drug out of its previously licensed use. In addition, with the extensive number of drugs in clinical practice, access to, and recall of, licensing information is difficult, since the ABPI Compendium is dense and comprehensive, and information about generic drugs is usually available only from the Medicines Control Agency by written application. Product Licence details also change from time to time and one cannot presume that information in a previous year's ABPI Compendium still pertains. It is thus surprisingly difficult and time-consuming to ascertain whether many of the drugs we commonly use are licensed for the way in which we administer them.

It is also clear that for drugs which have a Product Licence, the limitations imposed are frequently out of step with current good clinical practice, and sometimes absurd (see Marcaine® + adrenaline – Q2) or even dangerous (see thiopentone – Q3). The Product Licence cannot, therefore, be viewed as a reliable

guide to good, or even safe, practice. Whilst a manufacturer with a strong commercial interest in a particular drug may invest adequately in research to allow for Product Licence amendments to bring it in line with clinical practice, this appears to be a relatively rare occurrence. The investment required to demonstrate safety in pregnancy means that few drugs are licensed for use in pregnancy. Manufacturer's Specials (e.g. intravenous magnesium sulphate, physostigmine) are all unlicensed and may well be used only infrequently but for specific indications. However, as recently highlighted, the lack of commercial incentive to maintain the supply of relatively cheap, small turnover, drugs may threaten their future availability.<sup>12</sup> The fact that they are unlicensed may expose them to further censure by trusts or the Department of Health. We should beware of attempts to remove such drugs from hospital formularies.

Clinicians are caught in a dilemma. Good practice is likely to be based on interventions supported by evidence from clinical research, but many of the therapeutic options suggested by contemporary research may not be licensed. Doctors, therefore, commonly and willingly expose themselves to taking full responsibility for adverse effects from prescribing what they believe to be in the best interests of the patient. Hospital trusts, however, who also take responsibility (and may be liable) for the medical staff they employ, may view this from a different perspective. The increased potential liability associated with the use of drugs outside Product Licence may encourage trusts to attempt to minimize this practice, something several audience members appeared to have already experienced (Q12). The complexities of the subject suggest that even attempting to determine which drugs are used, for what, and by whom, in an unlicensed way is a virtually impossible task. Trusts should be made aware of the immense impact that implementation of a 'licensed drug administration only' policy would have. In anaesthesia it would severely limit all elective, emergency and obstetric interventions, and produce a crude, less safe, less reliable service. This cannot be of benefit to patients.

The basis of a defence against a claim of negligence is comparison of performance against what a 'reasonable body' of the defendant's peers would have done, and despite recent challenge, the 'Bolam' test remains well established.<sup>13</sup> In a 1995 editorial, Mather and O'Kelly suggest that either the Association of Anaesthetists or the Royal College of Anaesthetists should seek a role in the area of unlicensed drug administration, providing a 'reasonable body of opinion' and issue periodic guidance on what constitutes 'reasonable' drug practice.<sup>14</sup> A majority of OAA members expressed a similar view, that the OAA should

either publish the results of a current practice poll of members, or issue guidelines on reasonable drug practice in obstetric anaesthesia, or both.

However, whilst providing support for clinicians whose practice (of unlicensed drug administration) falls within such guidelines, several problems arise. Who should draw up such a set of guidelines and based on what information, and how often would it be updated? The medico-legal constraints that such a list is likely to impose might be counter-productive to good or innovative medical practice. In considering approval for the use of drugs outside their usual application (for example nitroglycerine for retained placenta, intrathecal neostigmine for analgesia) it may be hard to distinguish the practice of a maverick (support undesirable) from that of an expert, or a leader in the field (support desirable). Both inclusion and omission from the approved list may cause difficulties. Drug practice that is considered reasonable for a super-specialist may not be deemed so for a less knowledgeable, less specialised practitioner, and inclusion in an approved list of reasonable drug practice may not be deemed appropriate. In addition, if 37% of obstetric anaesthetists at the 1997 OAA Annual Meeting report having used propofol in pregnancy (Q4), does this constitute a reasonable body of opinion and support further use?

It is the opinion of the authors that whilst initially seeming to be useful, the production of national or local guidelines or formularies on reasonable drug practice, with their inherent medico-legal consequences, would be unhelpful both to the profession as a whole, and to patients. Medical practitioners are, and must surely always remain, answerable for their own individual practice. However, practitioners and their indemnifiers face an uphill struggle if unlicensed drug use is involved. In addition, it is unclear whether patients should be told if they are prescribed an unlicensed drug (although it rarely happens in current practice). Mather and O'Kelly discuss the role of the 'prudent doctor' test with respect to this aspect of informed consent.<sup>14</sup>

So what should be done to improve this rather contradictory situation, and where do we go from here? In the first place, awareness of both the extensive nature and clinical value of unlicensed drug administration in contemporary medicine needs widespread dissemination. Clinically inappropriate Product Licence details need review, since they do not serve in the patient's best interest. At best, they are ignored by clinicians (for example bupivacaine 0.5% with adrenaline for epidural analgesia in labour), and at worst they may put the patient at significant risk (for example thiopentone 250 mg maximum dose and technique). Development of an 'Orphan Drug Program', such as exists in the USA and Australia, would help the licensing of small cir-

lation, limited use drugs, where pursuit of a Product Licence would not otherwise be financially viable. However, some other process of authorising commonly used, clinically effective drugs and techniques would be helpful. Meta-analysis of trials performed under clinical trial exemption certificates could be useful in some circumstances.

At the time of writing, publication of the 'Medicines Act Letter 14' by the Department of Health is imminent. This directive is expected to address issues relating to completely unlicensed drugs (i.e. Specials and Prepared Medicines), although whether it will be helpful to clinicians is unclear. Further open discussion about this turbulent subject is needed to clarify the limits (if any) within which we are asked to practise. Perhaps it is even time to question the overall value of a proscriptive licensing system, which is so widely ignored by clinicians, and explore other possible solutions?

#### ACKNOWLEDGEMENTS:

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