EDITORIAL

THE SAFETY OF NEW DRUGS

The introduction of a new drug into anaesthetic practice may generally be regarded as beneficial: to the anaesthetist who hopes that old techniques may be improved or new ones developed, to the pharmaceutical company which hopes to expand its business and make a profit for its shareholders, and to the patient who hopes that his prospects for surviving the hazards of surgery may be improved.

Before the drug can be offered for sale, the company must obtain a product licence from the statutory Licensing Authority. In the case of human medicines this is the Minister for Health, advised by the Committee on Safety of Medicines. The application for such a licence is based on an exhaustive submission which demonstrates that the new product is:

- exactly what it says it is (i.e. the chemical structure can be proved, and a reliable synthetic pathway demonstrated),
- of satisfactory purity, such that it is not contaminated by reagent residues or unwanted synthetic products, especially those which might have some toxic or pharmacological effects,
- free from significant toxic effects in at least two species of laboratory animals,
- pharmacologically effective and free from significant adverse effects in laboratory animals,
- pharmacologically effective and therapeutically beneficial in man,
- free from hazardous adverse effects in man, when used according to the manufacturer’s recommendations. This requires evidence of a large database containing records of all adverse effects, obtained during the clinical trial stages.

Such applications are examined by the Committee on Safety of Medicines (CSM) and its two specialist subcommittees: Chemistry and Pharmacy (CPS) and Safety, Efficacy and Adverse reactions (SEAR). The procedures, which include a complex appeals machinery, may be quite protracted, and generally continue until the Committee is persuaded that its rigorous criteria have been satisfied.

Based upon a successful submission, the company must publish a Data Sheet, which sets out the range of licensed applications for the drug, the recommended methods of administration and dosage, relative and absolute contraindications, and possible adverse effects. On obtaining a product licence the Company must, under the provisions of the Medicines Act (1968), make the data sheet freely available to prescribers. All such data sheets are published regularly in a “Data Sheet Compendium” by the Association of the British Pharmaceutical Industry (ABPI).

Quite frequently, licences for entirely new products are limited in scope. Prescribers must be well aware of the range of licensed applications for new drugs, because the manufacturer’s liability is limited to usage within those terms. For instance, Diprivan (propofol) is recommended:

"...for induction and maintenance of general anaesthesia for surgical procedures which generally do not exceed one hour in duration".

The data sheet states quite clearly:

"...Experience in procedures lasting more than one hour is limited."

Then, in a later paragraph:

"...At this stage there is no experience of Diprivan in children or in mothers who are breast feeding".

If, then, a clinician decides to anaesthetize a 4-yr-old patient for a free tissue graft transfer procedure expected to take at least 6 h using a continuous infusion of propofol as the sole agent, but discovers that recovery is not as rapid as he had hoped, he could not legitimately complain that the data sheet had failed to warn him of this possibility.

As experience with a new drug increases, and the scope of clinical trials extends to special groups of patients (such as those at the extremes
of age, and those suffering from particular diseases), the manufacturer may submit further evidence to the CSM in order to extend the scope of the product licence. Thus we find that the data sheet for the long-established opioid Operidine (phenoperidine) suggests that it may be used both during anaesthesia and in the intensive care unit, where the indication is stated to be: “...as a respiratory depressant/analgesic in patients requiring prolonged assisted ventilation in intensive care units”.

By contrast, the much newer opioid Rapifen (alfentanil) is stated by the same manufacturer to be more restricted in use: “...a potent, narcotic analgesic with a very rapid and short-lived action. This makes it especially suitable for use as an adjunct to anaesthesia” “...may also be administered to ventilated patients undergoing longer operative procedures...” —but no mention of intensive care. This does not imply that alfentanil is ineffective in this role; quite the reverse. It is simply that the manufacturer has not yet submitted sufficient evidence to satisfy the CSM that alfentanil is both effective and safe for prolonged administration to critically ill patients.

As already stated, the submission for a product licence includes a substantial safety database, which should give a good indication as to the nature and severity of common adverse effects. However, there are two principal limitations. First, the database is compiled from information gained from highly structured clinical trials. As such trials are designed to demonstrate new virtues or throw light upon specific problems, they do not always have much in common with routine clinical practice. Thus we may see adverse effects appearing more or less frequently, and new side-effects may emerge. Second, the value of a new drug may eventually rest upon the incidence of unusual or even rare adverse effects; the continuing debate as to the clinical usefulness of halothane is a good example. The incidence of unusual adverse drug reactions (ADR) cannot be established from a safety database containing only a few hundred clinical records, and can only emerge as a result of closely monitored clinical use in a large number of patients.

Through its Safety, Efficacy and Adverse Reactions subcommittee (SEAR), the CSM monitors closely the ADR associated with each new drug. All new products are marked in the Data Sheet Compendium and MIMS Monthly Index of Medical Specialties with an inverted black triangle. This indicates that all ADR, however trivial, should be reported to the Committee. These reports are entered into the CSM's Adverse Reaction Register which is, in fact, a large computer database. At monthly intervals, all additions to the database are considered by the Adverse Reactions Group of SEAR (ARGUS).

In addition, all reports from anaesthetists are reviewed by the Joint Working Party. By such close monitoring, it is expected that unsuspected ADR will be detected in the shortest possible time. Currently, “black triangle” products of direct interest to anaesthetists include Diprivan (propofol), Nalorex (naltrexone) and Anexate (flumazenil).

It is hoped that the new “Anaesthetic Yellow Card”, designed by a joint working party of the College of Anaesthetists, the Association of Anaesthetists and the Committee on Safety of Medicines and now generally available, will facilitate the reporting of Adverse Drug Reactions occurring in anaesthetic practice. These have already been circulated widely, and further supplies can be obtained from:

The Committee on Safety of Medicines
Market Towers,
1, Nine Elms Lane,
London SW8 5NQ

or: call CSM freephone.

The present CSM spontaneous reporting scheme is an effective means of detecting infrequent ADR, but because there is no measure of the number of patients treated it does not give any reliable indication of incidence. Measures of incidence are of the utmost importance, as they may establish clinical preferences on a correct basis, rather than the time-honoured “trial by personal experience” which leads us all to have different perceptions of drugs according to our individual observations.

The true incidence of ADR can be assessed only by large-scale surveillance of both usage and occurrence. In this issue we publish two coordinated surveillance studies of atracurium, which report on data gathered in the U.S.A. [1] and Great Britain [2]. The American database contains data from 1013 patients given atracurium and 851 given other neuromuscular blocking drugs, while the British database contains records
of 477 patients given atracurium and 484 given vecuronium. As both studies used identical criteria devised by the Boston Collaborative Drug Surveillance Program, it is possible to make realistic estimates of the relative incidences of the various adverse effects associated with neuromuscular blockers.

The results may surprise readers, and will oblige many, including the author, to revise their perceptions of atracurium. Contrary to expectation [3], the incidence of histamine-related side-effects associated with atracurium are shown to be no more common than with other myoneural blockers. In the British study, "histamine-related" side-effects, such as rash or wheezing, occurred in only 1% and 0.4%, respectively, of atracurium patients, compared with 0.4% and 0.8% of patients given vecuronium. Among American patients given atracurium, only 0.3% developed rash and 1.5% wheezed, compared with 0.1% and 1.8% given other blocking drugs. Possibly histamine-mediated hypotension was equally uncommon in all patients in both studies.

In terms of overall safety, 86.7% of atracurium administrations were entirely uneventful, compared with 87.5% with other drugs in the U.S.A. The comparable figures from the British study were 71% and 60%, respectively. Neither study demonstrates any consistent difference between atracurium and other drugs in the same class.

To reassure those who may regard a 20.2% overall incidence of "possibly drug-related adverse events" as disturbingly high, it must be emphasized that only 3.6% were categorized as "major". Furthermore, this incidence represents the sum of all possible adverse effects from ALL the drugs used in relaxant anaesthesia, and necessarily includes a host of physiological responses to surgical events, which very often cannot be distinguished from true drug-related effects.

These results should be considered alongside those from an even larger study carried out in Australia and reported recently in this Journal [4]. Atracurium was given to 1845 patients and alcuronium to 1420. Most patients were allocated their drug by random selection, but a number of renal failure patients were given atracurium selectively. Notwithstanding that, the two groups were very similar, with closely matched ages, weights, sex distribution and type of surgery. The incidence of atopy was similar in both groups (14.2% v. 14.3%). The only notable difference was in the greater proportion of ASA III–V patients given atracurium (21.6% v. 11.5%).

In common with the Boston Collaborative Studies, the Australian results were surprising to many, and confounded a long-standing Anti-podean preference for alcuronium as the non-depolarizing neuromuscular blocker of choice. Instead of confirming this view, the results show convincingly that, while atracurium causes a higher incidence of local skin reactions (2.5% v. 1.5%), the incidence of hypotension was lower (3.4% v. 13.7%). Of even greater clinical significance, only one patient developed severe hypotension (defined as > 50% decrease in systolic pressure) after atracurium, compared with 11 patients after alcuronium. Overall, the incidences of "possible or probable" ADR were 10.1% for atracurium and 17.9% for alcuronium.

The combined database of 6106 patients enables the incidence of quite unusual events to be estimated. Of course, it is possible that even rarer events remain undetected, so that an even larger database will be needed before we can be quite sure that they do not. Nevertheless, taken together these large studies convey a clear and important message to clinical anaesthetists: there is no foundation whatever for any lingering suspicion that atracurium causes adverse reactions more frequently than other neuromuscular blocking drugs.

It is hoped and expected that, in future, all new drugs will be subjected to such searching analysis. Quite apart from any other reason, it is only by such means that their superiority (or otherwise) over those already available can really be demonstrated.

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REFERENCES