After practolol

Still licking its wounds from the mauling of a hostile public reaction to the apparent delay in medical recognition of the serious side effects of practolol, the pharmaceutical industry dominated the audience last week at the Medico-Pharmaceutical Forum’s meeting on postmarketing surveillance. The industry’s concern is shared by academic clinical pharmacologists and indeed by all clinicians, who have seen the practolol affair used by some propagandists to attack high-technology medicine; while there has been a far wider call for stricter controls on the release of new drugs. In the past twelve months an international workshop has been held on the topic in Honolulu (see p 1592) and no fewer than four schemes have been suggested for monitoring the incidence of side effects from new chemical entities. Much of the London meeting was concerned with a debate on the relative merits of these proposals.

On average about 2000 patients will have been exposed to a new drug at the time it is cleared by the Committee on Safety of Medicines. The rationale of postmarketing surveillance is that monitoring side effects on a further 10 000 or so patients should pick up any rare or unexpected reactions missed in the premarketing trials. Nevertheless, when the CSM has made further monitoring by the manufacturer a condition of licensing a product, the results have been disappointing. Dr S F Sullivan gave the meeting details of 25 drugs which had been evaluated by the company concerned, using medical representatives to recruit volunteer general practitioners. Despite financial incentives, in practice few doctors had been able to provide enough patients and fewer still had gone on to follow them up long enough or in adequate detail. Not surprisingly, these attempts at monitored release had not detected any new side effects of clinical importance—and they had proved inordinately expensive, averaging about £100 000 for every 1000 patients monitored. The difficulty in persuading doctors to add to their paperwork was, indeed, seen as the main drawback to the scheme proposed by Professors C T Dollery and M D Rawlins for special prescription forms for new drugs. Both Professor D H Lawson and Dr Alan Wilson, of the ABPI, preferred to rely on the NHS prescribing arrangements to pick out new drugs and so refer the forms to a central agency. This agency could then initiate follow-up inquiries from the doctors concerned (and possibly the patients) should any clinical suspicions be aroused.

Nevertheless, as Dr S Shapiro (Boston Drug Epidemiology Unit) pointed out, even if the numbers of patients monitored were increased to 20 000 such schemes would not detect some really important adverse effects. He cited the marrow aplasia associated with chloramphenicol (about 1 in 30 000 cases), the slow development of chloroquine retinopathy, the occurrence of vaginal adenocarcinoma in the offspring of women treated during pregnancy with stilboestrol, and the association between oestrogens as hormone replacement therapy and endometrial carcinoma as examples that would not have been detected by the new proposals. Several different schemes, he believed, needed to be designed to deal with hazards to the fetus, the neonate, the teenager, the pregnant woman, and the adult; more use should be made of hospital-based follow-up (pioneered by the Boston Collaborative Drug Surveillance Program) and of record linkage schemes such as the Oxford system. Dr D C G Skegg was less pessimistic. His own recent analysis of the early clinical experience with practolol had shown that eye symptoms had been reported to general practitioners but had not been recognised as side effects. What was needed, he argued, was for clinical trial protocols to require the recording of events without any judgment being made on causation. A patient who broke a leg while taking a drug might have been ataxic or osteoporotic as a side effect of the treatment or it might have been a coincidence; but if the event was recorded it would soon become apparent whether or not there was any true association.

No one challenged that view: indeed, there was general agreement that clinical observation and alertness remained the most important means of identifying unsuspected drug associations. Data collection did, however, have a valuable contribution to make, said Dr W H W Inman, the Principal Medical Officer, CSM. How helpful it would have been in sorting out the possible association between reserpine and breast cancer, for example, had there been on record the prescription forms of 10 000 patients given the drug when it had first been introduced. There was no doubt of the potential importance of identifying such a cohort for each new drug as it came on to the market—and such a procedure need not be expensive.

At the end of the day, then, no magic solution had been found that could guarantee that future drugs would be free of serious, unexpected adverse effects. Closer attention to the recording of events (rather than side effects) in clinical trials would help, and there seemed an overwhelming case for some system of recording and storing details of the patients given each new drug as it comes on to the market. The extent and length of their follow-up would then be determined by an assessment of individual clinical reports—and these, as they
have always done, will continue to depend on every prescribing doctor’s maintaining a high index of suspicion. The past year’s explosion of interest in monitoring has generated constructive proposals; the next stage—before the CSM takes any final decisions—should surely be for the practicability of one or more of the schemes to be assessed in pilot studies.

3 Lawson, D H, and Henry, D A. British Medical Journal, 1977, 1, 691.

More about infant diarrhoea

In 1972 the infant mortality rate from gastroenteritis in Britain1 was higher than in any other country in the European Economic Community except Italy (and possibly Luxembourg). In that year 297 children aged less than 1 year died of diarrhoeal disease in England and Wales. Since then, however, the mortality has fallen2 to 255 in 1973, 144 in 1974, and 120 in 1975. In Newcastle upon Tyne, for example, the incidence of severe dehydration and hypernatraemia in children admitted to the gastroenteritis unit has been drastically reduced between 1971 and 1975, and physicians there believe the explanation is an increase in breast-feeding and the introduction of low-solute milks.3

Experience at the gastroenteritis unit of the Queen Elizabeth Hospital for Children, London, in 1971 and 1972 has recently been reviewed,4 re-emphasising several important points. Firstly, only two of the 608 children seen there with gastroenteritis were breast-fed compared with 14%, of matched infants in the community served by the hospital, showing yet again the supreme importance of breast-feeding in the prevention of this disease. Secondly, the social origins of the disease were again evident. Multiple hospital admissions, lower social class, and “social problems” were common characteristics of affected children. Thirdly, the age of the child was an important determinant of the severity of the illness. Babies aged less than 6 months were much more likely to suffer serious biochemical disturbance, and the eight deaths in the series were all in children under this age, all but one being less than 2 months. Five of the deaths were in children with other serious abnormalities, four of whom had major congenital abnormalities.

Most babies with diarrhoea will recover after a short period of oral feeding with a glucose-electrolyte mixture (72% of children in this London series were not given intravenous fluids and only 3% of those having diarrhoea had been fed milk after the reintroduction of milk feeds). The management of the minority whose diarrhoea is prolonged may be difficult, and another recent analysis, this time of experience at the Hospital for Sick Children, London, gave useful practical advice.5 There were 82 infants with diarrhoea lasting for more than two weeks. A diagnosis was made in 59 (70%), the most common being coeliac disease, secondary disaccharide intolerance, and cows’ milk protein intolerance, though 12 patients had less common diseases and the full list of differential diagnoses included 28 possibilities. Prolonged diarrhoea dating from birth is a peculiar and difficult problem; of six such patients four died and a known cause for the diarrhoea was found in none. All were given prolonged intravenous nutrition, since they could not be fed by mouth. In two of these children there was a family history of similarly affected siblings who died, and another two were siblings with agenesis of the corpus callosum. No patient died whose diarrhoea did not date from birth. In the 59 patients whose diarrhoea had a specific cause long-term management was usually dictated by the diagnosis, but parenteral nutrition was sometimes necessary at first. Seventeen infants had diarrhoea not dating from birth for which no cause could be shown, but none of these needed parenteral feeding.

When faced with an infant with persisting diarrhoea most paediatricians will progress through a variety of milks beginning with a lactose-free milk such as Galactamin 18, followed by one which is lactose free and contains either altered cows’ milk proteins (Nutramigen) or only soya bean protein (Velactin, Pro Sobee). Children fed with most special milks (but not Nutramigen or Pro Sobee) need added vitamins and these can best be provided as Ketovesi liquid and tablets. (Liquid and tablets are different and complementary.)

For difficult, undiagnosed, prolonged diarrhoea various synthetic and semisynthetic diets have been advocated, but none has been entirely satisfactory. The Great Ormond Street team6 had considerable success with a fluid diet based largely on comminuted chicken—all 17 infants with non-specific diarrhoea not dating from birth responded to it promptly.

If, indeed, the life-threatening complications of gastroenteritis have become less common with the introduction of low-solute milks and with renewed efforts to promote breast-feeding it may be possible in future to avoid admission to hospital in all but a few cases, though in young babies under the age of 6 months close and careful supervision will be necessary if they are to be nursed at home. Only a small minority of babies will have persisting diarrhoea, but these require specialised investigation and care in hospital.


Chemotherapy in bladder cancer

Bladder cancer accounts for much of a urologist’s work load and requires not only the co-operation of radiotherapists, chemotherapists, and pathologists but also the use of costly technological resources. Experience has shown that clinically there is a clear separation between two parts of the range of urothelial cancer.1,2 Some 80% of the lesions are papillary, non-invasive, T1 lesions; the remaining 20%, are solid, invasive cancers classed as T2, T3, and T4. In both types the end results leave little cause for satisfaction or complacency.

The five-year survival3-5 for T1 lesions is about 70-80%. Nevertheless, as over half of these papillary cancers are multiple and recurrent, diagnosis and treatment require repeated cystoscopies under general anaesthesia. Here the main problem is preventing recurrence—and knowing what to do when the recurrences are too frequent and too numerous to be controlled by endoscopic surgery. We need more trials