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Hazards of non-practolol beta-blockers

Some of the adverse reactions from beta-adrenoceptor antagonism are predictable.[1] These include bradycardia, heart block, cardiac failure, bronchospasm, hypotension, cold extremities, claudication, Raynaud's phenomenon, diarrhoea, fatigue, weakness, muscle cramps, dizziness, hallucinations, vivid dreams, and sleep disturbance. Sudden withdrawal may precipitate "cardiac events" in patients with severe ischaemic heart disease. Signs of hypoglycaemia may be masked. Interactions may occur with other drugs. Many other minor symptoms have been described, usually in patients treated with propranolol—the first of this class of drugs, available for over 11 years, and the one with which prescribers have the greatest body of experience.[1]

Most beta-blockers seem to be equally effective, provided that equipotent doses are given[3]; and predictable adverse reactions are likely to be similar if equivalent doses are compared. Their possession of membrane-stabilising (local anaesthetic or quinidine-like) activity or of partial agonist (intrinsic sympathomimetic) activity is probably clinically unimportant at conventional oral dosages. A cardioselective action should not be misinterpreted as a cardiospecific effect, and caution is necessary when prescribing for patients at risk. The incidence of predictable adverse reactions to individual beta-blockers also depends on the route of administration, dose, frequency of administration, elimination characteristics, and patient factors. Patients who are dependent on adrenergic drive should not be given beta-blockers. Patients with cardiac, respiratory, hepatic, renal, metabolic, or psychiatric disease are also at increased risk, particularly if they are receiving concurrent treatment with other drugs.[1]

The recognition of the oculomucocutaneous syndrome associated with practolol[4–6] and its subsequent withdrawal from general use raise two important questions. The first concerns the cause of this unexpected syndrome, in its full form characterised by a rash, eye lesions, secretory otitis media, sclerosing peritonitis, pleurisy, and pericarditis. No convincing explanation is yet available, though its seems likely that the syndrome is due to a specific chemical effect of practolol or a metabolite, and there may be a predisposed group of patients. The relevance of concurrent disease processes and of concomitant drug treatment has yet to be established. The group of 16 patients with practolol peritonitis described recently[7] had been taking the drug for at least 15 months, and all patients had lesions in organs other than peritoneum. LE cells, antinuclear factor, and antibodies to DNA were not found. In two patients the onset of abdominal symptoms occurred eight months after practolol had been stopped.

The other important question is whether beta-blockers other than practolol may be associated with the development of the oculomucocutaneous syndrome. With world-wide sales figures of over £100 million this question is of concern to patients, doctors, and the pharmaceutical industry. Clearly doctors must report any suggestive suspected adverse reactions to the drug regulatory authorities, such as the Committee on the Safety of Medicines. Similarly, drug companies who market beta-blockers must ensure close surveillance of their products. Some companies have been suspected of dragging their feet in reporting adverse reactions, especially unconfirmed reports.[2] Doctors, too, seem slow to report predictable reactions to newly introduced agents. An early answer is required, because the beta-blocker group undoubtedly represents one of the more important advances in cardiovascular therapy.[8]

The practolol syndrome was not detected until the cumulative experience with the drug had totalled one million patient years. This delay occurred because practitioners were not aware of the syndrome and so were not looking for it or recognising it. Furthermore, widescale use of a drug seems to be necessary before unexpected and unpredictable adverse reactions can be recognised. As Dollery and Rawlins[2] have pointed out, the yellow warning cards of the Committee on Safety of Medicines are of little use in detecting previously unrecognised adverse drug effects. Now that this particular adverse effect is known, however, there should not be any similar delay should other beta-blockers cause the syndrome. The suggestion that newly marketed beta-blockers should be monitored by a computer-assisted registered release system[2] has the attraction that routine independent objective and expert evaluation of adverse reactions to new drugs could be obtained. Yet such a system would also suffer from some of the recognised limitations of existing drug surveillance systems: the variable quality of the information recorded about the drug prescribed, the influence of concurrently prescribed drugs, and the contribution of associated diseases. In addition, the assessment of adverse reaction questionnaires depends on the personality of the patient and doctor and on the design of the questionnaires.

The present state is therefore one of alert but not of alarm. It seems unlikely that the unpredicted and unexpected

practolol oculomucocutaneous syndrome is the direct result of beta-blockade, because propranolol has been available for over a decade and there has been no validated report of propranolol-induced sclerosing peritonitis[7] or eye lesions. Chemical differences exist between different beta-blockers, and pharmacokinetic studies also show differences,[1] so that careful and continuing evaluation of all reported adverse reactions is essential, and premature conclusions must not be drawn—many patients have pre-existing unrecognised skin or eye disease. Reports of skin reactions confirm that beta-blockers, like many other drugs, are associated with rashes of various kinds.[9,10] So far, however, none of the patients on propranolol or oxprenolol who have developed rashes have had the typical practolol-like oculomucocutaneous syndrome. Similarly the findings of Marshall *et al*[7] that some patients on treatment with propranolol or oxprenolol developed radiological abnormalities of the small bowel should be interpreted with caution: no patient treated with oxprenolol or propranolol alone has been shown to have sclerosing peritonitis.

Ahlquist conceived the concept of alpha- and beta-adrenergic receptors in 1948. Recently he has written that practolol has a serious delayed adverse reaction,[3] which is unique. Patients, doctors, and the pharmaceutical industry must hope that this assessment is correct.

[1] Petrie, J C, *et al*, *Postgraduate Medical Journal*, 1976, **52, suppl 4,** 63.
[2] Dollery, C T, and Rawlins, M D, *British Medical Journal*, 1977, **1,** 96.
[3] Ahlquist, R P, *Progress in Drug Research*, 1976, **20,** 27.
[4] Wright, P, *British Medical Journal*, 1975, **1,** 595.
[5] Brown, P, *et al*, *Lancet*, 1974, **2,** 1477.
[6] Felix, R H, Ive, F A, and Dahl, M G C, *British Medical Journal*, 1974, **4,** 321.
[7] Marshall, A J, *et al*, *Quarterly Journal of Medicine*, 1977, **46,** 135.
[8] Shand, D G, *New England Journal of Medicine*, 1975, **293,** 280.
[9] Padfield, P L, *et al*, *British Medical Journal*, 1975, **1,** 626.
[10] Cumberbatch, J B St C, *British Medical Journal*, 1974, **4,** 528.

Monkeypox and smallpox in Africa

Monkeypox was first recognised in 1958 in a captive monkey colony,[1] and at least ten further outbreaks were reported in the next decade. Four occurred in monkeys captured in Malaysia, but a search for virus in wild monkeys there failed, and no naturally occurring disease has been reported. Since 1970 there have been 20 cases of monkeypox in man reported from West and Central Africa. In 13 instances the virus was isolated and recognised by electronmicroscopy, while in others the laboratory diagnosis was serological.[3] The clinical picture was very similar to that of smallpox, except that the vesicular fluid was exceedingly viscid, and four patients died. In only four cases was there a possibility of person-to-person transmission. Primary smallpox vaccination carried out in some patients who had suffered monkeypox produced little reaction—a finding that might have been expected from a closely related vaccine.

Extensive epidemiological investigations have been conducted in the areas where the human cases were reported. Serum with or without tissues from 3400 animals, mostly monkeys, yielded no monkeypox virus, but antibody was found on several occasions; the poxvirus inducing the antibody could not be determined. Viruses as yet indistinguishable from variola virus were isolated from the kidneys of six healthy monkeys and two rodents; these have been termed "whitepox viruses." Experimental inoculation of this virus into a monkey did produce a generalised rash.

A survey of five million children has since been carried out in West Africa. Although some had pockmarks of smallpox contracted before 1970 (the year of the first report of monkeypox in man and of the last report of smallpox in West Africa), none of the children had any pockmarks attributable to any smallpox-like illness since 1970.

Smallpox transmission seems, therefore, to have been interrupted in Africa, and an animal reservoir of variola virus has not been identified. Monkeypox in monkeys has so far been recognised only in those in captivity and seems not to be a great danger to man. The importance of whitepox virus to animals and man is unknown, but its isolation has been a rare event.

[1] von Magnus, P, *et al*, *Acta Pathologica et Microbiologica Scandinavica*, 1959, **46,** 156.
[2] Arita, I, *et al*, *Bulletin of the World Health Organisation*, 1972, **46,** 625.
[3] Arita, I, and Henderson, D A, *Bulletin of the World Health Organisation*, 1976, **53,** 347.
[4] Foster, S O, *et al*, *Bulletin of the World Health Organisation*, 1972, **46,** 569.

Multiple sclerosis

The cause of multiple sclerosis (MS) is most likely to be discovered by a multidisciplinary research effort. The January issue of the *British Medical Bulletin*[1] took that approach to bring the medical profession up to date on most aspects of the disease. After a short and relevant introduction the clinical features are described and an attempt is made to rationalise the nomenclature, incorporating the results of some of the recent advances, especially in electrophysiological tests, such as visual, auditory, and somatosensory evoked responses. As the *Bulletin* reminds us, however, the results of all such tests should be used in their clinical context.

The epidemiology section confirms the known relation of the prevalence of MS to latitude by birthplace for persons of north and central European origin. The frequency of the disease appears to be associated with HLA type distribution; and, if (as seems likely) Orientals, many south Europeans, and black Africans prove to be relatively insusceptible, genetic variation might explain much of the geographical distribution of the disease. Lack of information on the incidence of the disease in the people of southern Europe and South America is holding back this aspect of research into MS.

In reviewing the pathological features of MS one chapter attempts to relate the various types of lesions seen to the possible mechanisms of pathogenesis. Though leaving a lot of questions unanswered, it sets out clearly what the problems are in this field and points out lines of research which would be rewarding to follow. The account of the pathophysiology of demyelinating disease will be of particular interest to the electrophysiologist. The increased sensitivity of demyelinated fibres to temperature changes is fascinating, and the clinician will be interested to relate the findings in this chapter to his patient's experience of the effects of heat and cold on his clinical state. The section on the immunological and biochemical diagnosis of MS makes the point again that a combination of tests gives the best results. The oligoclonal pattern of the gammaglobulin subfractions in the cerebrospinal fluid (CSF) is said to be the most helpful single indicator, followed by estimation of IgG in the CSF in the