Highlights from an International Symposium

Non-Narcotic Analgesics Today
An Update on Benefits and Risks

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Comparing the Pharmacology of Non-Narcotic Analgesics

Despite non-narcotic analgesics being the most widely used drugs and many having been used for several decades, their generally ascribed mechanisms of action are not unequivocally accepted, Professor *K. Brune*, of the University of Erlangen-Nürnberg, Erlangen, West Germany, told his audience. Most non-narcotic analgesics are derived from aspirin and other acidic non-steroidal anti-inflammatory drugs (NSAIDs) , aniline derivatives such as paracetamol (acetaminophen) and non-acidic pyrazolones. Many of these drugs have stood the test of time and have demonstrated efficacy with an accepted profile and incidence of side effects. It is important, stressed Professor Brune, to consider clinically relevant pharmacodynamic and pharmacokinetic properties of analgesics to identify their specific advantages and disadvantages. He used aspirin, paracetamol, ibuprofen and dipyrone (metamizole) as long established examples to illustrate his approach. Aspirin and ibuprofen are particularly useful in alleviating pain related to inflammation, whereas dipyrone appeared particularly effective in spastic pain and paracetamol less active than the others as an analgesic. Dipyrone and paracetamol are widely used as antipyretics.

Important pharmacokinetic characteristics of non-narcotic analgesics in man were rapid and reliable absorption, near complete bioavailability, adequate distribution without preferential concentration in organs associated with side effects, rapid elimination by the kidneys and liver, and a low propensity for drug interactions. Although all non-narcotic analgesics complied with these ideals to some extent, they were not equally suitable for routine analgesia. A long and variable elimination half-life reduced the usefulness of piroxicam and phenylbutazone, and delayed absorption decreased the value of some others.

In returning to the 4 example drugs, Professor Brune pointed out that salicylic acid, a metabolite of aspirin, and 4-methylaminoantipyrine, the active metabolite of dipyrone, reached almost 100% bioavailability, whereas paracetamol and ibuprofen did not. The requirement for reliable elimination from the body was not met by all 4 example drugs since salicylic acid cumulation may follow high doses of aspirin. Impaired kidney or liver function may aggravate this risk and elimination of paracetamol may be prolonged in patients with decreased liver function. Such reductions in the efficiency of elimination do not interfere with ibuprofen, whereas their influence on dipyrone is not known.

Of the 4 drugs, only aspirin appears to bear the risk of potentially serious drug interactions, said Professor Brune. However, none is without side effects and each causes specific potentially serious effects on rare occasions, although few epidemiological studies are available to confirm their incidence. The prolonged inhibition of platelet aggregation by aspirin necessitates its avoidance in patients with blood clotting disorders and, like ibuprofen, in patients with peptic ulceration. Patients whose intolerance of aspirin appears as bronchoconstriction should avoid ibuprofen (and

other NSAIDs). Dipyrone should be used for only a few days in the elderly, who seem more likely to develop type I agranulocytosis, and paracetamol is best avoided in alcoholics. Professor Brune suggested that analgesic mixtures should be avoided in the treatment of pain, since their efficacy and risks had never been subjected to epidemiological scrutiny.

Pulmonary Side Effects of Non-Narcotic Analgesics: Allergy and Pseudoallergy

The important aspects of allergic and pseudoallergic reactions to non-narcotic analgesics were presented by Professor *B.A. Peskar* of Ruhr-University, Bochum, West Germany, who concentrated on the relatively rare pulmonary reactions to these drugs. Some patients react to the ingestion of non-narcotic analgesics with bronchoconstriction and asthmatic attacks, although an allergic mechanism was responsible in only a few of these. In the majority the basis for the pulmonary side effects was pseudoallergic. Several hypotheses have been advanced to explain the molecular mechanism of pseudoallergy, said Professor Peskar, including drug-induced stimulation of kinin receptors, activation of the complement system and interference with eicosanoid biosynthesis. The latter hypothesis is attractive, he said, because inhibition of fatty acid cyclo-oxygenase seems to be an important property of the non-narcotic analgesics and could explain why susceptible persons exhibit similar sensitivity to drugs of different chemical structure.

It remains unknown, however, said Professor Peskar, whether the crucial drug effect on arachidonic acid metabolism is inhibition of synthesis of a bronchodilating eicosanoid such as prostaglandin E_2 or diversion away from cyclo-oxygenase products towards increased synthesis of bronchoconstricting leukotrienes. The latter explanation was considered attractive by Professor Peskar, who pointed out that increased leukotriene formation and simultaneous inhibition of prostaglandin synthesis by various NSAIDs, including high concentrations of pyrazolones and paracetamol, had been observed in macrophages. However, none of the hypotheses explained why only a minority of patients with predisposing conditions experienced pulmonary side effects.

Professor Peskar then addressed the practical therapeutic aspects of the two types of reaction by reminding his audience that, whereas patients with true allergy need avoid only the specific allergens, pseudoallergic aspirin-sensitive patients should avoid all NSAIDs that are effective inhibitors of cyclo-oxygenase. If such patients require treatment with anti-inflammatory drugs, aspirin desensitisation can be tried. It should be remembered, however, continued Professor Peskar, that after desensitisation patients remain asthmatic and require regular therapy.

Renal Toxicity of Non-Narcotic Analgesics

Professor *P. Kincaid-Smith,* from the University of Melbourne and The Royal Melbourne Hospital, Australia, told her audience that the renal toxicity of non-narcotic analgesics involves acute, subacute and chronic damage. Information on the renal effects of aspirin and NSAIDs in healthy subjects is conflicting, but in high renin states, reductions in glomerular filtration rate and renal plasma flow have been reported consistently. Oedema is the most common symptom associated with the administration of therapeutic doses of NSAIDs, being more pronounced in patients with underlying renal disease or high renin states. Hyperkalaemia, which may be life-threatening is associated with decreased plasma renin and aldosterone, and has most often occurred during indomethacin treatment of gout.

Acute renal failure, as distinct from the nephrotic syndrome, is probably caused by haemodynamic changes and often reverses rapidly after withdrawal of the drug. This acute deterioration in renal function usually occurs in patients with underlying renal disease in whom maintenance normal renal circulation depends on an adequate secretion of prostaglandin E_2 and prostacyclin. Other predisposing factors include advancing age, high renin states, gout, renal artery stenosis and, particularly, concomitant diuretics. Although acute renal failure has been attributed to many NSAIDs, Professor Kincaid-Smith said that its incidence appears to correlate with the consumption of any particular drug in a community. The frequent implication of phenylbutazone may, she suggested, be connected with its uricosuric activity.

The greatest interest in acute renal failure associated with NSAIDs has related to acute interstitial nephritis; the nephrotic syndrome, which commonly occurs in patients with previously normal renal function, appears after 2 to 18 months of drug treatment, recovers slowly after drug withdrawal and is probably an idiosyncratic reaction. In two-thirds of reported cases, fenoprofen has been implicated, zomepirac and tolmetin being suspected most often among the other widely used NSAIDs. The pathology of this subacute syndrome has attracted much interest, said Professor Kincaid-Smith, the changes resembling those of lipoid nephrosis.

The two chronic clinical syndromes discussed by Professor Kincaid-Smith, analgesic nephropathy and uroepithelial carcinoma, have been attributed to long term abuse of analgesic mixtures. Analgesic nephropathy, which is essentially a chronic progressive form of renal papillary necrosis, has a major incidence in countries where caffeine-containing powders are sold widely 'over the counter' and taken in large amounts, and occurs often in patients with rheumatoid arthritis. In such patients renal papillary necrosis is found frequently at autopsy and in a study conducted by Professor Kincaid-Smith there was either macroscopic or microscopic evidence of the syndrome in over 80% of cases. Initially, analgesic nephropathy was attributed to phenacetin, but the unabated mortality from the syndrome subsequent to phenacetin restriction in some countries and the gradual decrease in end-stage renal failure from analgesic nephropathy following regulated sale of analge-

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sic mixtures containing aspirin, paracetamol, caffeine, salicylamide or phenacetin, supports the contention from experimental studies that other analgesics are at least partly responsible. Professor Kincaid-Smith reiterated that abuse of analgesic mixtures has also been implicated in uroepithelial tumours, which are found most often in females, but that this relationship has not always been confirmed.

Role of Prostaglandin Synthesis Inhibition in NSAID-Associated Renal Syndromes

In an appropriate sequel to the description of clinical syndromes associated with the renal toxicity of NSAIDs, Professor *C.A.Patrono* from the Catholic University School of Medicine, Rome, Italy (Visiting Professor at the Royal Postgraduate Medical School, University of London, England) explained the role of prostaglandin synthesis inhibition in their pathogenesis. He pointed out that, while there was adequate information causally relating drug-induced changes in renal function to concomitant decreases in prostaglandin synthesis, such data do not provide unequivocal proof that inhibition of renal prostaglandin synthesis leads to the development of chronic renal injury. It is now generally accepted that prostaglandin synthesis in the kidney is localised to specific sites and that prostaglandins synthesised in the cortex (primarily PGI_2; prostacyclin) regulate cortical function (mesangial relaxation and contraction, vasodilatation and vasoconstriction), while those synthesised in the medulla (PGE_2) regulate medullary function (excretion of sodium chloride and water). Measurement of urinary unmetabolised prostaglandins or their stable hydration products by radioimmunoassay provides the best clinical assessment of the state of renal prostaglandin production.

Professor Patrono explained that in healthy persons, renal function is not critically dependent on intact renal cyclo-oxygenase activity, whereas under a variety of clinical conditions such as volume depletion, congestive heart failure, cirrhosis with ascites and the nephrotic syndrome, inhibition of modulatory prostaglandin activity by drugs that inhibit renal cyclo-oxygenase can acutely reduce glomerular filtration rate and renal blood flow by 30 to 50%. Administration of aspirin, but not of sodium salicylate, reduced urinary PGE excretion and a similar effect occurs with most commonly used NSAIDs - except sulindac - when given at full anti-inflammatory dosage, said Professor Patrono. Few data are available on the effects on renal prostaglandin synthesis of the pyrazolones, pyrazolidines or *p*-aminophenol derivatives. Some of the mechanisms proposed by Professor Patrono to explain the selective sparing of renal cyclo-oxygenase included differential sensitivity of renal cyclo-oxygenase, differential rate of recovery of glomerular cyclo-oxygenase after irreversible inactivation (as occurs with low

dose aspirin), and selective intrarenal inactivation of an active metabolite of a drug (as occurs with sulindac).

The long term consequences of renal prostaglandin synthesis inhibition are more difficult to assess, stressed Professor Patrono, although theoretically such inhibition might be responsible for medullary ischaemia possibly contributing to the picture of analgesic nephropathy. Furthermore, the long term consequences of selective versus non-selective cyclo-oxygenase inhibition remain unknown. The infrequency of renal syndromes associated with sulindac compared with their somewhat higher incidence in patients treated with other NSAIDs suggests that reduced renal prostaglandin synthesis bears a cause-effect relationship to the reported functional changes. However, he pointed out, the disproportionate involvement of fenoprofen in the NSAID-induced nephrotic syndrome indicates that mechanisms other than inhibition of renal prostaglandin synthesis may contribute to the nephrotoxic potential of any drug.

Risk of Ulcer Complications with NSAIDs

Professor *M.J.S. Langman* from the Queen's Medical Centre, Nottingham, England, presented the findings of a recently completed case-control study, which determined the risk of peptic ulcer complications among users of aspirin and other NSAIDs. He pointed out that the conflicting data produced over the years, suggesting that the risk of upper gastrointestinal bleeding or perforation associated with anti-inflammatory drug intake could be either negligible or substantial, arose largely because of inadequate controls. Early retrospective case-control studies which appeared to show a substantial risk of gastric bleeding associated with aspirin intake failed to compare the drug intake of patients with that of individuals in the community. Since the reasons for analgesis intake were also not considered in these studies, it was conceivable that patients would be taking the analgesic to relieve ulcer pain. In such circumstances, subsequent gastric bleeding would not be caused by the analgesic intake. Professor Langman and his colleagues set out to overcome these study design deficiencies by choosing age- and sex-matched community controls and by using paracetamol as a positive control. Analysis of the derived data indicated that about one-third of aspirin intake in patients with bleeding is equivalent to that in controls and is by deduction non-causal; another third, by reference to parallel increases in paracetamol intake, represented drug intake consequent upon the presence of the bleeding lesion and was thus also non-causal. The remaining third was unexplained and likely to be causal.

As regards NSAIDs, Professor Langman stated that the perception of clinicians has been that such drugs were commonly associated with upper gas-

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trointestinal bleeding and with ulcer perforation. However, he said, there has been no unanimity about the likely causal drugs and no properly controlled studies that enabled calculation of the risk. Again determined to right this situation,Professor Langman, by including matched community controls and limiting comparisons to individuals aged 60 years or more, was able to show that the riks of ulcer complications among such individuals treated with NSAIDs were appreciable. Assuming that the findings in the Nottingham population were representative of those generally in the United Kingdom, there might be about 2000 cases of bleeding induced by NSAIDs each year in the total UK population. The insubstantial risk of ulcer complications suggested by postmarketing surveillance studies has arisen, said Professor Langman, because the apparently large case series studieed are dwarfed by the general extent of prescribing and because such surveys have not concentrated on those at greatest risk - the elderly.

Role of Leukotrienes and Prostaglandins in NSAID-Induced Acute Gastrointestinal Mucosal Damage

An overview of the experimental evidence examining the role of prostaglandins and leukotrienes in the acute damage of the gastric mucosa induced by non-narcotic analgesics was presented by Professor *B.M. Peskar* of Ruhr-University, Bochum, West Germany. Since gastrointestinal tissues have a high synthesising capacity for prostaglandins (PG), some of which have been shown to protect the gastrointestinal mucosa against potentially harmful substances, it has been suggested that the generation of prostaglandins is crucial in maintaining mucosal integrity.

The hypothesis that aspirin and like substances disrupt the gastric mucosal barrier, thus promoting back diffusion of acid into mucosal tissue, has been overshadowed by another well supported hypothesis that inhibition of cyclo-oxygenase, and consequently of prostaglandin synthesis, reduces the capacity of the gastric mucosa to resist injury. This is supported by experimental studies in which the concomitant administration of PGE_2 and aspirin reduced the overt mucosal damage and microbleeding relative to that induced by aspirin alone. NSAIDs which inhibit both gastrointestinal and systemic prostaglandin production cause gastrointestinal mucosal damage, whereas those drugs that inhibit systemic prostaglandin synthesis (reduced concentration of circulating PGmetabolite ketodihydroprostaglandin $F_{2\alpha}$), while having minimal effect on gastric PGE_2, are less ulcerogenic. In this context, Professor Peskar pointed out that paracetamol, which does not inhibit gastrointestinal prostaglandin formation, causes no damage to gastric mucosa, whereas aspirin and indomethacin inhibit gastrointestinal prostaglandins and are more damaging to the mucosa. Factors such as tissue-specific differences in the sensitivity of cyclo-oxygenase and pharmacokinetic properties modify the inhibi-

tory activity of analgesic and anti-inflammatory drugs on gastrointestinal prostaglandin formation.

The active metabolite of dipyrone (metamizole) has been found to minimally decrease gastrointestinal prostaglandins in some studies but not in other, and it was suggested by Professor Peskar that species or methodological differences may account for these findings. It was postulated that increased production of leukotriene C_4 might encourage gastric mucosal damage, since its stimulation by ethyl alcohol paralleled induction of mucosal ulceration, and inhibition of alcohol-stimulated leukotriene C_4 by carbenoxalone or a lipoxygenase inhibitor attenuated the mucosal damage. Although Professor Peskar considered that inhibitors of cyclo-oxygenase could increase leukotriene formation by shifting the substrate arachidonic acid to the lipoxygenase pathyway, she conceded that the role of leukotrienes in NSAID-induced acute gastrointestinal mucosal damage had yet to be established.

Liver Damage

The clear message from Professor *L.F. Prescott* from the Royal Infirmary, Edinburgh, Scotland, was that although the non-narcotic analgesics can produce a variety of hepatic lesions, clinically significant liver damage is uncommon with usual therapeutic use. The pattern of hepatotoxicity caused by the salicylates, NSAIDs, paracetamol and the pyrazolones differs, but many of these drugs can cause generalised reactions which involve the liver. Depending on the drugs in question, the risks of liver injury may be conditioned by factors such as age, sex, dose and duration of treatment. Hepatotoxicity associated with the use of salicylates and most NSAIDs has been reported most often in females with collagen diseases, but this may simply reflect the greater use of these drugs in such patients. Paracetamol-induced liver damage occurs almost exclusively as a result of overdosage.

Professor Prescott pointed out that pathological changes seen in hepatic reactions to non-narcotic analgesics are generally variable and nonspecific, except for the microvesicular fatty changes in hepatocytes of patients with Reye's syndrome attributed to salicylate, the acute centrilobular necrosis caused by paracetamol in overdosage, and the marked cholestasis produced by benoxaprofen. About half of the patients given salicylate develop minor abnormalities of liver function that are related to plasma salicylate concentration and are usually rapidly reversible. However, said Professor Prescott, in a small proportion of predominantly young patients, liver damage is more severe and closely resembles that seen with Reye's syndrome, which has a high mortality rate. Since the young seem particularly sensitive to the adverse metabolic and hepatic effects of salicylates, Professor Prescott suggested, provocatively, that aspirin not be given to children.

Professor Prescott reiterated that, in substantial overdosage, paracetamol can cause acute hepatic necrosis. Without specific treatment, some 8% of adults suffer severe liver damage and 1 to 2% die with hepatic failure and encephalopathy. The average acute single threshold dose for severe liver damage is about 250 mg/kg in adults but is probably greater in children. Severe paracetamol-induced liver damage is characterised by a dramatic increase in plasma aminotransferase activity up to 10,000 U/L or more, prolongation of the prothrombin time and a modest increase in plasma bilirubin concentration. Maximum abnormalities of liver function are delayed until the third day, after which recovery is usually rapid and complete. In very severely poisoned patients who do not receive early specific therapy, hepatic failure with encephalopathy may occur on the fourth to sixth days. Paracetamol causes liver damage by conversion to a reactive metabolite (N-acetylbenzoquinoneimine) which binds covalently to hepatic proteins and inactivates sulfhydryl-containing enzymes. Glutathione plays a crucial protective role by preferential conjugation with this metabolite: hepatic necrosis does not occur until glutathione is depleted. The administration of sulfhydryl compounds such as N-acetylcysteine within 8 to 10 hours effectively prevents liver damage and death, said Professor Prescott. Liver damage has been attributed to the therapeutic use of paracetamol but in most reports the dose was excessive and many patients were chronic alcoholics (who seem to be at increased risk). In these cases the features were typical of acute overdosage.

Liver damage has been reported with most NSAIDs and pyrazolone analgesics (butazones), but a consistent and characteristic pattern of hepatotoxicity is evident with relatively few. Professor Prescott emphasised that a rank order of relative risk cannot be established and the incidence in relation to use is not known. Benoxaprofen (now withdrawn) produced a characteristic syndrome which was often fatal, and over the years there have been many reports of hepatotoxicity with phenylbutazone after both therapeutic use and overdosage. Of the other drugs in these groups, glafenine, diclofenac, clomethacin, sulindac and pirprofen seem to carry the greatest risk of hepatotoxicity. The mechanisms are unknown.

Blood Dyscrasias Secondary to NSAIDs

In a presentation on blood dyscrasias secondary to NSAIDs, Professor *P.A. Miescher* from the Geneva University Hospital, Switzerland, told his audience that drug reactions may be classified as either reactions to the pharmacological properties of the drug or those caused by a drug-dependent immune mechanism. Reactions belonging to the first category seldom occur with NSAIDs and usually do so when the drug is given in excessive dosage or

to an individual who is highly susceptible to a certain pharmacological action. By far the largest proportion of NSAID-induced reactions is of the immune type, said Professor Miescher. He also commented that the risk of immunisation varies between drugs, those which are strongly bound to proteins being more likely to form drug-specific antibodies. The strongly bound pyrazolidines (butazones) are particularly prone to produce severe immunological complications. Once immunisation has occurred, re-exposure to the offending drug may lead to allergic reactions, the nature of which depends on the degree of sensitisation, the type of immune reaction and the *in vivo* half-life of the causative drug. Professor Miescher informed his audience that 5 different mechanisms can be distinguished: (a) IgE-mediated drug reactions, (b) IgG- and IgM-induced blood cell damage, (c) passive agglutination-type mechanism of drug-induced blood cell damage, (d) partial autoantibody-induced drug reactions and, finally, (e) drug-induced autoantibody formation.

Professor Miescher continued with a discussion of the haematological side effects of NSAIDs according to the mechanisms by which they produced agranulocytosis, thrombocytopenia, haemolytic anaemia, aplastic anaemia or pure red cell anaemia. In the 1920s, aminopyrine was found to cause agranulocytosis characterised by a rapid onset with flu-like symptoms. This type I agranulocytosis is rapidly reversible provided that the drug is stopped upon appearance of the early symptoms (sore throat). The pyrazolidines (butazones), phenothiazines and chloramphenicol, on the other hand, produce agranulocytosis of either type II or a mixed type. After drug withdrawal, recovery from type II agranulocytosis is slower than from type I, and the prognosis less favourable. The acetic acid derivatives indomethacin, sulindac, tolmetin and zomepirac have occasionally been implicated in agranulocytosis, as have other NSAIDs including fenoprofen, fenbufen, ibuprofen, naproxen and mefenamic acid. Thrombocytopenia, like agranulocytosis, can be divided into types I and II, explained Professor Miescher, with type I having the faster recovery. Indomethacin, clomethacin, sulindac and tolmetin, have most often been associated with thrombocytopenia. Haemolytic anaemia, a less common side effect, has been reported with methyldopa and mefenamic acid, but the autoantibody production seen with these drugs is rarely found with other analgesics.

The most serious haematological reaction is aplastic anaemia, said Professor Miescher, since it causes the highest mortality. Fortunately, however, its incidence is low. Current data suggest the involvement of immune phenomena and that it is more likely to develop with drugs producing type II agranulocytosis than with those involved in type I. Professor Miescher reminded those present that the side effects of the various drugs must always be considered in relationship to their total consumption as well as to the population at risk. There was a tendency for physicians to incriminate the newest drug in a patient who developed a blood dyscrasia, but in many instances a causal relationship could not be established. It is hoped, concluded Professor Miescher, that future careful evaluation of adverse drug reaction reports will provide a more accurate incidence of blood dyscrasias occurring with the implicated drugs.

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Prescription Event Monitoring

A large scale attempt to link exposure to selected drugs, identified by means of prescriptions, with subsequent events recorded in patients' case records was described by Mr. *N.S.B. Rawson* from the Drug Surveillance Research Unit, Southampton, England. Patients being treated with any of the 4 drugs monitored at any one time are identified manually by the Prescription Pricing Authority. The identity of the selected drugs is not revealed until receipt of the required number of prescriptions. A maximum of 4 questionnaires, known as 'green forms', are sent to any one doctor who indicates when the drug was first prescribed and for what indication, its efficacy, and any events which occurred during or after treatment. Such events are not restricted only to those thought to be due to drugs. Since the scheme began in 1982, about 200,000 'green forms' relating to one or other of more than 12 drugs have been received by the unit.

The results of studies with 5 NSAIDs, benoxaprofen, zomepirac, slow release indomethacin ('Osmosin'), fenbufen and piroxicam, were presented by Mr Rawson, who stated that as the first 3 drugs mentioned had been withdrawn from the market before monitoring began, the study concerned the follow-up period of 4 to 18 months. Osteoarthritis, the most common indication, accounted for 18% of patients taking zomepirac and 46 to 48% of those using the other drugs. Rheumatoid arthritis was treated more often with benoxaprofen than with any of the other drugs, while zomepirac was often used as an analgesic in terminal cancer. Mr Rawson considered the rate of reporting within this voluntary scheme to be good,with 57 to 68% of mailed questionnaires being returned. Derived data clearly illustrated the tendency of benoxaprofen to cause photosensitivity, rash, onycholysis and nail changes. Gastrointestinal events occurred with similar frequency for all 5 drugs and there were only 4 deaths from peptic ulcer complications among the 55,642 patients studied. One of the pitfalls of assessing the events was highlighted with the example of the persistently high incidence of dyspepsia and gastritis after cessation of 'Osmosin', a drug developed to decrease such events in patients who experience gastrointestinal symptoms with other NSAIDs.

It is important to remember, said Mr Rawson, that the prescription event monitoring system described will identify only those events which occur in at least 1 in 1000 patients. Although the service was criticised for failing to measure the incidence of benoxaprofen-induced fatal hepatorenal disorders, it did detect these conditions in patients treated with benoxaprofen.

Intensive Medicines Monitoring Programme in New Zealand

A description of a postmarketing surveillance scheme conducted in New Zealand and known as the Intensive Medicines Monitoring Programme (IMP), was presented by Professor *I.R.Edwards* from the University of Otago, Dunedin, New Zealand. This programme was instigated to monitor for 3 years medicines selected because of their novel chemistry or pharmacology, their relationship to other drugs which previously caused clinical problems,or their potentially extensive usage.

Originally, pharmacists were requested to record details of the patient and prescribing doctor, the medicine,the dose and the duration of the prescription, each time a prescription for a selected drug was dispensed. Concurrently, prescribing doctors were asked to forward details of any unexpected clinical events, whether or not they believed them to be medicine-related. Unlike in the programme described by Mr Rawson, doctors and pharmacists are advised of the drugs currently on the IMP.

The usual rate of returns from pharmacists is about 80%, but from doctors is about 5%, and there is a tendency to report apparent reactions requiring cessation of treatment rather than events. The main reasons for non-reporting, said Professor Edwards, were the 'Seven Deadly Sins' previously described by professor W. Inman-complacency, fear of litigation, guilt, ambition, ignorance, diffidence and lethargy. In an attempt to improve on this poor response, data linkage systems, and a special self-carbonated duplicate prescription form to be used only for IMP medicines, have been introduced. The inclusion of an event indicator box to be ticked by the doctor has enabled active follow-up by the Medical Assessor's office of all positive responses and has resulted in a 15-fold increase in event reporting. Consequently, the duplicate prescription system will be introduced throughout the country over the next 3 years.

Drugs monitored by the scheme have included mianserin, nifedipine, captopril and amiodarone, but unfortunately, said Professor Edwards, no non-narcotic analgesics have been studied. Thus far, the IMP has alerted doctors to new events requiring active follow-up, led to the establishment of adverse drug reaction profiles, and indicated risk/benefit relationships. Despite the potential for abuse of confidentiality, this inexpensive system has been running successfully for 10 years.

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Serious ADRs Associated with Non-Narcotic Analgesics

An estimate of the risk of serious adverse events or death associated with non-narcotic analgesic administration, based on data from clinical experience in West Germany, was presented by Professor *H.Kewitz* of the Freie Universität Berlin, West Germany. Professor Kewitz reiterated the point made by other speakers, that the real incidence of serious ADRs associated with analgesic use can best be determined by case-control epidemiological studies. In an example of hospital derived data, Professor Kewitz indicated that 1% of 6000 patients referred to the medical department had experienced a serious ADR attributed to analgesic ingestion. These patients were from a population of 200,000 to 300,000 served by that hospital. Among another group of 6000 inpatients, who received analgesics during their stay in hospital, ADRs were noted in 4.5 to 8.2% of those treated with paracetamol, indomethacin or aspirin and in 1% treated with dipyrone (metamizole) or tilidine. Gastrointestinal side effects were reported most frequently.

Professor Kewitz referred briefly to the international case-control study on agranulocytosis and aplastic anaemia (I.S.A.A.A.), which involved a total population of 19.5 million people in 7 countries followed over a period of 5 years. While the results of this study are yet to be published, preliminary findings suggested that the incidence of agranulocytosis was 6 per year per million of population while the incidence of aplastic anaemia was half this value. The proportion of these blood dyscrasias due to analgesic use is not clear, but since the overall mortality among patients with agranulocytosis was 5%,the risk is low. In another study involving 3649 patients with colic pain, the frequency of bronchospasm or shock within 48 hours of injection of pyrazolones, opioids or other analgesics was 0.2% to 0.5%.

It was stressed by Professor Kewitz that although only some of the reported events were attributable to analgesic use, no reliable differentiation between disease-related and drug-induced effects could be achieved. A multiple logistic regression analysis which considered patient's age, sex, severity of colic, hospital admission and concomitant use of other drugs, revealed no significant differences between the drug groups. None of the 7 deaths that occurred was related to drug treatment. From these data, Professor Kewitz concluded that serious ADRs to analgesics, usually 'allergic', occurred in 2 in 1000 patients.

The Regulatory Challenge

The challenge for drug regulatory authorities is to strike a balance between what is ideally desirable and that which is reasonably attainable within the limits set by resources and usefulness, said Professor *P.K.M. Lunde* of the University of Oslo, Norway. The major objective is to protect the public by selecting the safest possible and most cost-effective drugs and by ensuring that such drugs are used to greatest advantage. Regulators face many influencing factors, including the sometimes conflicting interests of politicians, the medical professions, teaching institutions, pharmaceutical manufacturers and consumers. In addition, the lay press and mass media increasingly voice a variety of interests and opinions,the influence of which-along with the other forces-varies both between and within countries. While the regulatory bodies clearly acknowledge the rights of individuals to make up their own minds, those authorities must be careful that attitudes alone do not form the basis for regulatory actions or medical practice.

It must always be remembered, said Professor Lunde, that drugs are not a substitute for deficient health services, and that drugs-although usually considered beneficial-may be harmful if inappropriately used and promoted. For example, he said, some fixed dose combinations are so imbalanced in their content or include such a large number of ingredients, that they greatly increase the risk of toxic or hypersensitivity reactions. Professor Lunde reiterated that there is a fine balance between restrictive and constructive measures, since the flourishing private drug and health sector must be contained while promoting a credible public health sector and some degree of confrontation with the vested interests is inevitable.

If it is to be effective, a drug regulatory agency must enlist the participation of the appropriate professionals and consumers, representing expert skills and common sense. There is a constant need for global collaboration and communication within and beyond the field of drugs and for improving the education of health professionals and the public. Politicians must not be given the impression, said Professor Lunde, that any drug-and therapy-orientated problem can be solved simply by allocation of sufficient resources.

Progress has been made, and there is now available a draft model WHO curriculum on national drug policy and rational drug use, for critical testing within universities and other institutions responsible for the education of health workers. In concluding, Professor Lunde said that it is vital that any national drug policy retain sufficient flexibility so that decisions can be modified in the light of subsequent experience.

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Regulatory Decisions and the Consumer

An insight into what the British consumer can reasonably expect of their drug regulatory authorities was provided by Professor *M.D.Rawlins* of the University of Newcastle Upon Tyne, England. While consumers can reasonably expect regulatory judgements on drug quality, efficacy and relative safety for prescription drugs, and finer judgement on these drugs from their prescribers, with OTC medicines consumers must rely on the professional judgement of regulatory authorities. Thus, said Professor Rawlins, the safety of OTC products must be well established and of greater magnitude than for prescribed medicines.

The five principal consumer expectations at the time of marketing are that (a) a drug should be of good quality; (b) it should have an established efficacy for its claimed indications; (c) it should have satisfied the regulatory authorities'standards of safety; (d) it should have undergone professional assessment of benefit/risk; and (e) doctors should have been adequately informed of how best to use the drug and be aware of any potential problems evident on the basis of available data. Additionally, consumers expect to be protected from extravagant promoter claims of efficacy and safety. Once a drug is marketed, there is the obvious consumer expectation of continued surveillance by the regulators to re-evaluate benefit/risk ratios, which at present is being achieved by means of spontaneous reporting systems.

With the NSAIDs, said Professor Rawlins, ADR reports represent a comparatively high proportion of total reports; 20 to 30% of those received by the Committee on Safety of Medicine between the years 1977 and 1981. Such reports followed a clear pattern, being high during the first year of introduction and gradually declining with time, both in total and as events per million prescriptions. In descending order of frequency, NSAID-induced events involve the gastrointestinal tract, liver, blood, skin and kidneys. When examining spontaneous ADRs, regulatory authorities look for novel effects, such as anaphylaxis with zomepirac which led to its subsequent withdrawal; risk factors such as age, dose, duration of treatment; and, controversially, use reports to make comparisons between available NSAIDs. Although controversial, such use of these data has shown that during the first 5 years of marketing of 13 NSAIDs, the number of reports per drug has varied from 275 down to 13 per million prescriptions. The 3 drugs associated with a high reporting rate were withdrawn from the market, but not without some controversy, said Professor Rawlins. At the other end of the scale, ibuprofen is now available as an OTC product. There are several sources of bias which confound the interpretation of these data, including potential aberrations caused by careful postmarketing surveillance studies for some drugs but not others, special claims for safety by the manufacturers, and adverse publicity which may increase the reporting rate for a particular drug.

Finely-tuned judgement needs to be exerted by prescribing doctors when the balance between safety and efficacy is unclear or when close patient monitoring is needed to avoid toxicity, and only when extensive and prolonged clinical experience indicates such judgement to be unnecessary can the consumer expect wider and more convenient OTC availability with appropriate labelling.

Decision-making and the Regulatory Bodies: Viewpoint from Sweden

A regulatory authority view of the adequacy of the Swedish system of assessing risk associated with drug administration was presented by Professor *K. Strandberg* of the National Board of Health and Welfare, Uppsala, Sweden. He stressed that to be effective, postmarketing surveillance of drugs must be customised for the specific problems of that country. He outlined the approaches used in Sweden, where spontaneous ADR reporting data and those from drug utilisation and patient-and disease-orientated registers have provided much useful information on safety problems with different drugs.

The registers, which provide information from the whole or a random sample of the population, involve relatively simple reporting techniques, and include total sales, prescription sample, diagnosis and therapy, mortality, cancer, malformation and patient registers. The cost of obtaining this information is low, since it is collected primarily for other purposes such as health care planning. The system of spontaneous ADR reporting is well supported by Swedish physicians, as reflected by reports of the Guillain-Barre syndrome associated with zimeldine. While acknowledging the advantages and disadvantages of the spontaneous reporting system, Professor Strandberg said that the number of reports had increased consistently to the present level of around 3000 per year. Although under-reporting and selective reporting were also generally considered to be disadvantageous, the latter had been advantageous in identifying risk factors in glibenclamide-induced hypoglycaemia.

In touching upon the controversial subject of using ADR data for comparative analyses among related drugs, also discussed by Professor Rawlins, it was pointed out by Professor Strandberg that while one school of thought holds the view that spontaneous ADR reports should not be used at all for comparative analyses, his department considered these reports to be hypotheses generating and so leading to some cautiously monitored comparisons. In one such instance an apparently excessive incidence of ADRs associated with phenformin was shown to be erroneous after phenformin was restricted and the subsequent increase in metformin usage was found to be

accompanied by a parallel increase in ADRs. However,since lactic acidosis and fatal reactions remained more frequent with phenformin, and no difference in patient characteristics was detected from the prescription survey, it was decided to withdraw phenformin from the Swedish market in 1978.

Monitoring of the available NSAIDs over several years has revealed ADR profiles that are qualitatively similar, although quantitative differences with respect to skin, liver and central nervous system effects were evident with some drugs. Professor Strandberg stressed, however, that the data generated are not able to determine whether or not the findings are genuine reflections of the inherent properties of the drugs. He also warned that those people who insist on conclusive scientific validation should realise that to accomplish this before any action is taken may be impossible, usually because of the time required.

The greatest disadvantage with the patient and disease registers, said Professor Strandberg, is the frequently inaccurate diagnoses, whereas a general disadvantage is the delay in obtaining the data, ranging from about 3 months for the drug utilisation register to an unacceptable 3 to 4 years for the cancer register. The available systems are very useful, and can be improved by further education of physicians and complemented by provision for initiation of case control studies when problems indicate their necessity.