CSM UPDATE

Non-steroidal anti-inflammatory drugs and serious gastrointestinal adverse reactions—2

CSM Update is a regular monthly column written by members and staff of the Committee on Safety of Medicines.

THE MOST COMMON severe adverse reactions to non-steroidal anti-inflammatory drugs reported to the CSM are those affecting the gastrointestinal tract (haemorrhage and perforation), but substantial numbers of reports have also been received of blood dyscrasias and of serious reactions affecting the liver (hepatitis, jaundice, hepatic necrosis, hepatic failure), kidney (renal failure, glomerular and interstitial nephritis), and skin (epidermal necrolysis, exfoliative dermatitis, Stevens-Johnson syndrome). Table I shows the number of serious gastrointestinal reactions to all non-steroidal anti-inflammatory drugs available from 1964 to 1985, and, for each drug, the combined number of serious reactions affecting the blood, liver, kidney, and skin.

Apart from the obvious excess of reports of "other serious reactions" (mainly of aplastic anaemia and agranulocytosis) with phenylbutazone and oxyphenbutazone, the crude totals in table I provide little basis for comparing individual drugs. The number of adverse reaction reports to a product is related to its use, and unless some account is taken of the size of the exposed population it may be grossly misleading to compare products. Moreover, adverse reaction reporting rates for a drug tend to be highest during the first year or two of marketing and then decline. Any comparisons between non-steroidal anti-inflammatory drugs must take these and other factors into account.

TABLE I—*Number of reports (deaths in parentheses) of serious gastrointestinal reactions (haemorrhage, perforation) and other serious reactions (liver, kidney, skin, blood)*

Drug (year marketed)	Serious gastrointestinal reactions	Other serious reactions	Total serious reactions
Aspirin (1899)	192 (71)	26 (7)	218 (78)
Phenylbutazone (1952)	222 (71)	688 (326)	910 (397)
Mefenamic Acid (1963)	26 (1)	167 (21)	193 (22)
Indomethacin (1964)*	324 (126)	226 (48)	550 (174)
Oxyphenbutazone (1965)	13 (3)	241 (116)	254 (119)
Ibuprofen (1969)	218 (29)	163 (15)	381 (44)
Alclofenac (1972)	2 (0)	15 (2)	17 (2)
Naproxen (1973)	336 (40)	138 (21)	474 (61)
Ketoprofen (1973)	225 (17)	42 (3)	267 (20)
Fenoprofen (1974)	82 (9)	56 (11)	138 (20)
Azapropazone (1976)	150 (22)	64 (3)	214 (25)
Sulindac (1977)	37 (7)	62 (2)	99 (9)
Flurbiprofen (1977)	140 (15)	43 (5)	183 (20)
Feprazone (1978)	23 (0)	61 (5)	84 (5)
Diflunisal (1978)	122 (11)	49 (3)	171 (14)
Fenclofenac (1978)	23 (4)	61 (5)	84 (9)
Diclofenac (1979)	126 (17)	99 (2)	225 (19)
Tolmetin (1979)	4 (0)	4 (0)	8 (0)
Fenbufen (1980)	72 (4)	74 (7)	146 (11)
Piroxicam (1980)	641 (62)	121 (12)	762 (74)
Benoxaprofen (1980)	113 (19)	219 (58)	332 (77)
Zomepirac (1981)	68 (3)	20 (4)	88 (7)
Tiaprofenic Ac (1982)	55 (6)	6 (0)	61 (6)
Indoprofen (1982)	50 (7)	0 (0)	50 (7)
"Osmosin" (1982)	170 (26)	8 (0)	178 (26)
Suprofen (1983)	9 (1)	1 (0)	10 (1)

*Excluding Osmosin brand of indomethacin.

Table II shows the number of reports of serious adverse reactions to some non-steroidal anti-inflammatory drugs during their first five years of marketing; the number of reports per million prescriptions are also shown. Since prescription data have been available (from the Prescription Pricing Authority) only since 1968, whereas yellow card reporting began in 1964, no comparable prescription related data are available for aspirin, phenylbutazone, oxyphenbutazone, mefenamic acid, and conventional preparations of indomethacin so they have been omitted from table II. Alclofenac is also left out as it was withdrawn for reasons additional to clinical toxicity. Post marketing data on some of these drugs are available for less than five years, either because the product was introduced after 1981 or because it was withdrawn.

DESPITE CONSIDERING PRESCRIBING volume and marketing life, the data in table II provide no estimate of *absolute* risk. The number of prescriptions overestimates the number of exposed patients because of repeat prescribing; yellow card reporting, even of serious reactions, is incomplete; and, since gastrointestinal haemorrhage and perforation occur commonly in people not taking these drugs, we cannot conclude with certainty that exposure to a non-steroidal anti-inflammatory drug is causally related to such a reaction in any individual patient.

The data can, however, be used to give an approximate estimate of the *relative* risk of various non-steroidal anti-inflammatory drugs, provided potential confounding factors are taken into account. Firstly, comparisons should be made only between products used for broadly similar clinical indications (zomepirac, although pharmacologically a non-steroidal anti-inflammatory drug, was marketed solely as an analgesic and has therefore been omitted). Secondly, there should be reasonable confidence that there is no significant reporting bias: this may occur when the medical press or the lay media have aroused interest in a particular drug, or when claims have been made that a product may be safer than others. In addition, when a drug has been subjected to a special postmarketing surveillance study adverse reaction reporting may be more complete than usual. Finally, when comparing drugs we need to remember that there was an overall increase in adverse reaction reporting rates in 1976-7.

TAKING INTO ACCOUNT all these potential confounding factors, the CSM believes that three broad conclusions can be drawn from a careful scrutiny of the data in table II.

- As a group non-steroidal anti-inflammatory drugs are an important cause of serious adverse reactions.
- The adverse reaction profile of individual drugs varies. Some cause predominantly gastrointestinal reactions while others have a greater effect on the blood, liver, kidney, or skin.

TABLE II—*Prescription related reports (deaths in parentheses) of serious gastrointestinal and other serious reactions (liver, kidney, skin, blood) to some non-steroidal anti-inflammatory drugs during their first five years of marketing*

Drug	No of serious gastrointestinal reactions	No of other serious reactions	Prescriptions (million)	Gastrointestinal reactions per million prescriptions	Other serious reactions per million prescriptions	Total serious reactions per million prescriptions
Benoxaprofen*	113 (19)	219 (58)	1·47	76·9 (12·9)	149·0 (39·5)	225·9 (52·4)
Fenclofenac	20 (3)	50 (3)	0·53	37·7 (5·7)	94·3 (5·7)	132·1 (11·3)
Feprazone	22 (0)	56 (5)	0·44	50·0 (0)	127·3 (11·4)	177·3 (11·4)
Indoprofen*	50 (7)	0 (0)	0·09	555·6 (77·8)	0 (0)	555·6 (77·8)
"Osmosin"*	170 (26)	8 (0)	0·44	386·4 (59·1)	18·2 (0)	404·5 (59·1)
Azapropazone	61 (7)	19 (2)	0·91	67·0 (7·7)	20·9 (2·2)	87·9 (9·9)
Diclofenac	68 (9)	60 (1)	3·25	20·9 (2·8)	18·5 (0·3)	39·4 (3·1)
Diflunisal	105 (8)	43 (3)	3·13	33·5 (2·6)	13·7 (1·0)	47·2 (3·5)
Fenbufen	56 (3)	53 (4)	1·57	35·7 (1·9)	33·8 (2·5)	69·4 (4·5)
Fenoprofen	54 (7)	19 (4)	1·67	32·3 (4·2)	11·4 (2·4)	43·7 (6·6)
Flurbiprofen	92 (7)	28 (4)	3·35	27·4 (2·1)	8·4 (1·2)	35·8 (3·3)
Ketoprofen	106 (5)	17 (0)	3·19	33·2 (1·6)	5·3 (0)	38·6 (1·6)
Naproxen	153 (19)	39 (7)	4·67	32·8 (4·1)	8·4 (1·5)	41·1 (5·6)
Piroxicam	538 (48)	86 (9)	9·16	58·7 (5·2)	9·4 (1·0)	68·1 (6·2)
Sulindac	33 (5)	42 (2)	1·38	23·9 (3·6)	30·4 (1·4)	54·3 (5·1)
Suprofen*	8 (1)	1 (0)	0·05	160·0 (20·0)	20·0 (0)	180·0 (20·0)
Tiaprofenic Ac*	45 (6)	3 (0)	0·60	75·0 (10·0)	5·0 (0)	80·0 (10·0)
Tolmetin	5 (0)	3 (0)	0·12	41·7 (0)	25·0 (0)	66·7 (0)
Ibuprofen	36 (3)	36 (1)	5·47	6·6 (0·5)	6·6 (0·2)	13·2 (0·7)

*Marketed for less than five years.

- The toxicity of marketed non-steroidal anti-inflammatory drugs varies between products, and the CSM considers that these drugs fall into three categories. Five products (benoxaprofen, fenclofenac, feprazone, indoprofen, and Osmosin (slow release indomethacin)) appeared to be substantially more toxic than others and have been withdrawn. One product (ibuprofen) appears to be less toxic, at least at low dosage, and is now available from pharmacies without prescription. In terms of overall safety the remaining drugs cannot be clearly distinguished from each other on the basis of yellow card reports. It is not yet possible to determine whether the apparent differences between these drugs are due to their toxicity or to confounding factors and reporting bias. Comparisons with suprofen are especially difficult because it is the newest of the drugs and postmarketing experience in Britain is therefore limited.

Further studies may establish whether some of these non-steroidal anti-inflammatory drugs are significantly more hazardous than others. The CSM will continue to monitor them but, for the present, emphasises its previous advice.

- Non-steroidal anti-inflammatory drugs should not be given to patients with active peptic ulceration.
- In patients with a history of peptic ulcer disease and in the elderly they should be given only after other forms of treatment have been carefully considered.
- In all patients it is prudent to start at the bottom end of the dose range.

As always, the committee wants doctors to send in yellow cards for all serious suspected adverse drug reactions with all non-steroidal anti-inflammatory drugs.

During the course of a year a woman has changed her eating habits to reduce calorie and animal fat intake and increase vegetable and fibre intake. She is now 12 kg lighter, happy, and healthy, but she is yellow, presumably because she eats a pound or more of carrots daily. Is carotenaemia harmful?

The received opinion is that carotenaemia is benign[1] and that the much quoted case of carrot juice poisoning was, in fact, due to chronic malnutrition. The intake of around a pound of carrots a day might provide intakes of up to 70 mg a day of carotenoids, and, although this is theoretically equivalent to nearly 12 000 μg retinol equivalents, the conversion to retinol is controlled to avoid the production of excessive retinol.[2] Interestingly, the acceptable daily intake of the sum of β-carotenoid food additives (E160) is set at 0·5 mg/kg body weight a day.[3] This patient is clearly consuming more than this from natural sources, although no toxicological effects have been cited.—D A T SOUTHGATE, head nutrition and food quality division, Food Research Institute, Norwich.

1 Davidson S, Passmore R, Brock JF, Truswell AS. *Human nutrition and dietetics*. 7th ed. Edinburgh: Churchill Livingstone, 1979:120.
2 Dagadu M, Gillman J. Hypercarotenemia in Ghanaians. *Lancet* 1986;i:531-2.
3 Scientific Committee for Food. *Food additive regulations*. (EEC) 2635/vi/75-E. 1975.

What is the preferred treatment for carcinoma of the prostate?

The preferred treatment of prostatic cancer should be individually directed to the particular patient with regard to the circumstances. In general terms treatment depends very much on whether the disease is confined to the prostate or has metastasised, while the age and general condition of the patient must also be considered. Most patients in the United Kingdom with carcinoma of the prostate present with local symptoms due to bladder outflow obstruction and the process of the disease is necessarily usually advanced. The local symptoms are relieved by a transurethral resection and if there are no metastases (bone scan negative and serum acid phosphatase normal) external beam radiotherapy to the prostate may be tried. If metastases are present the choice is between bilatral orchidectomy (preferably the cosmetically more acceptable subcapsular operation) or treatment with antiandrogens. Stilboesterol, even in low dosage, because of its adverse cardiovascular effects accentuated in the presence of concurrent or pre-existing cardiovascular disease prevalent in elderly men, is becoming a much less popular alternative method of treatment. Most urologists prefer to use cyproterone acetate, an antiandrogen with progestogenic activity, in a dose of 300 mg daily, taken as two 50 mg tablets thrice daily. More recently leuteinising hormone releasing hormone analogues given as monthly depot injections (Zoladex, ICI) or intranasally as a snuff (Buserelin, Hoëchst) are being investigated and evaluated against orchidectomy in randomised multicentre trials to be reported later this year. The concept of total androgen blockade using leuteinising hormone releasing hormone analogue with pure antiandrogen flutamide has been reported[1] and requires further evaluation.—J C GINGELL, consultant urologist, Bristol.

1 Labrie F, Dupont A, Belanger A, *et al*. A new approach in the treatment of prostate cancer, complete instead of partial withdrawal of androgens. *The Prostate* 1983;4:579-94.