A METHOD FOR PREDICTING THE PHOTOTOXICITY OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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- 1 The photosensitisation potential of several non-steroidal anti-inflammatory drugs (NSAIDs) has been investigated *in vivo* using an irradiation monochromator.
- 2 Evidence of abnormal, immediate photosensitivity was obtained in 13 of the 38 patients taking one of four out of seven different NSAIDs.
- 3 A simple mathematical model was developed to predict the likelihood of photosensitivity occurring with a given drug by considering the mass of drug normally ingested, the spectral absorption characteristics of the drug, and the quantity and spectral quality of the radiation (e.g. sunlight) to which the patient may be exposed.

Keywords phototoxicity non-steroidal anti-inflammatory drugs

Introduction

The non-steroidal anti-inflammatory drugs (NSAIDs) have gained prominence in recent years as useful therapeutic agents in the management of rheumatoid and osteoarthritis. However several of these drugs have been reported as inducing adverse cutaneous photosensitive reactions (Committee on Safety of Medicines, personal communication). The photosensitisation potential of many of these drugs, particularly benoxaprofen, has subsequently been confirmed by laboratory investigation (Wiskemann, 1981; Kligman & Kaidbey, 1982; Ferguson *et al.*, 1982; Diffey & Daymond, 1983; Diffey *et al.*, 1983).

The clinical features associated with NSAID photosensitivity suggest a phototoxic, rather than photoallergic reaction (Halsey & Cardoe, 1982; Harber *et al.*, 1982). Theoretically, phototoxic reactions should occur in 100% of the population if sufficient doses of drug and appropriate wavelengths of light are present. Since only radiations which are absorbed are effective in promoting a photochemical change (first law of photochemistry) and hence photodermatological reactions, it is reasonable to suppose that the absorption spectrum of the drug *in vitro* will, to some extent, determine the photosensitising efficacy of the drug *in vivo*. The purpose of this study was to examine how this simple hypothesis can account for the photosensitive reactions seen in patients receiving treatment from this group of drugs. It is realised, of course, that several other factors may influence individual responses to phototoxic agents such as differences between individuals in pharmacokinetics and metabolism of the phototoxic agent, and

differences in skin pigmentation reflecting variations in the penetration of light into the skin.

The NSAIDs, although chemically distinct, share many common properties. The exact mode of action of each drug is not fully understood, but all these drugs are potent inhibitors of the enzyme prostaglandin synthetase (Simon & Mills, 1980). This property undoubtedly plays an important part in the anti-inflammatory effect, but there is no clearly defined relationship between the inhibitory potency of a drug against prostaglandin synthetase *in vitro* and clinical efficacy (Drug and Therapeutics Bulletin, 1981). This implies that other mechanisms of action are also likely to be involved.

Methods

In vivo study

Details of the *in vivo* study have been given elsewhere (Diffey & Daymond, 1983) but the main features are summarised below.

A total of 38 patients who were taking one of seven different NSAIDs for either osteoarthritis or rheumatoid arthritis were exposed to ultraviolet radiation (UVR) in a narrow wavelength interval around 320 nm. All patients had been taking the appropriate drug for at least 1 week at the time of phototesting. The type and normal dose of each of the drugs are listed in Table 1.

The apparatus used to irradiate the patients con-

Table 1 Summary of NSAIDs examined

Drug	Solvent	Extinction coefficient at 320 nm (bandwidth 10 nm), $\epsilon(\text{cm}^2 \text{mg}^{-1})$	Normal dose of drug, M (mg)
Benoxaprofen	0.1 N sodium hydroxide	100	600 once daily
Ibuprofen	0.1 N sodium hydroxide	~ 0	800 twice daily
Indomethacin	Methanol	17.5	75 twice daily
Ketoprofen	0.1 N hydrochloric acid	7	50 four times daily
Naproxen	Methanol	11.7	500 twice daily
Piroxicam	Methanolic 0.01 N hydrochloric acid	56.4	20 once daily
Tiaprofenic acid	Methanolic 0.1 N hydrochloric acid	48.8	200 three times daily

sisted of a 900 W xenon arc lamp optically coupled to a single grating monochromator. A liquid-filled light guide transmitted the radiation from the exit slit of the monochromator to the patient's skin (see Figure 1). The size of the irradiation field was 0.5 cm in diameter. All phototesting was carried out on the back of each patient as this anatomical site exhibits a higher sensitivity and more uniform response to ultra-

violet radiation than most other anatomical locations. Patients were irradiated at a wavelength of 320 nm (bandwidth 10 nm) since this spectral region of 310 to 330 nm was found to be most effective in producing abnormal photosensitivity in patients taking benoxaprofen (Ferguson *et al.*, 1982; Diffey & Daymond, 1983). Each patient was given a series of exposure doses ranging from 0.5 to 4 Jcm^{-2} in a geometric series.

Figure 1 A patient being investigated with the irradiation monochromator.

equivalent to doubling alternate exposures. The irradiation sites were examined immediately after exposure and the minimum radiation dose (in Jcm^{-2}) noted that produced the immediate reactions of urticarial weals, erythema and flaring around the site of irradiation, and sensations of itching and burning. Because of travelling difficulties experienced by several patients in this study, the threshold dose for delayed (24 h) erythema was not recorded.

In vitro study

Each of the seven NSAIDs were dissolved in a suitable solvent (see Table 1) to a concentration of 0.05 mg cm^{-3} . A small volume of each solution was transferred to a quartz cuvette (0.2 cm path length) and the absorption spectrum measured in the wavelength interval 290 to 400 nm using a scanning spectrophotometer (Pye Unicam SP8-150). A cuvette containing the appropriate solvent was placed in the reference beam.

In addition, the absorbance at 320 nm with a bandwidth of 10 nm was recorded since this spectral interval corresponds to that used for the patient irradiation. The extinction coefficient $\epsilon(\lambda)$ ($\text{cm}^2 \text{ mg}^{-1}$) at wavelength λ nm for each NSAID was calculated according to

$$\epsilon(\lambda) = A(\lambda)/cl \quad (1)$$

where $A(\lambda)$ is the observed absorbance at λ nm, c is the concentration in mg cm^{-3} , and l is the path length (cm) of radiation in the sample.

Results

In vivo study

Evidence of abnormal, immediate photosensitivity was obtained in 13 of the 38 patients taking one of

four of the NSAIDs (Table 2). In all 13 patients immediate erythema within the 0.5 cm diameter irradiation site and extending 1 and 2 cm around the site was seen. Nine of these 13 patients also exhibited an urticarial weal.

In vitro study

The absorption spectrum of each drug (apart from Ibuprofen which exhibits negligible absorption in the spectral range 290 to 400 nm) is shown in Figure 2.

The extinction coefficients at 320 nm for each drug calculated from the measured absorbance at this wavelength are listed in Table 1.

Discussion

This study has shown that several NSAIDs are capable of inducing adverse cutaneous photosensitive reactions. A simple model for expressing the photosensitisation potential of each drug in the spectral interval 310–330 nm would be in terms of the mass of drug normally ingested (M , mg), the extinction coefficient at 320 nm (ϵ , $\text{cm}^2 \text{ mg}^{-1}$) and the radiant exposure, or dose (H , Jcm^{-2}), such that we can define a photosensitivity index (PI) as

$$PI = M\epsilon H \quad \text{Joules} \quad (2)$$

Hence, at each radiant exposure (H) it is possible to calculate a value of PI and the corresponding probability of inducing a cutaneous photosensitive reaction. These data are summarised in Table 2 for all adverse photosensitive reactions observed here. The 95% confidence interval of the estimated probability was taken from the relevant tables assuming a binomial distribution for the number of patients experiencing an adverse reaction at a given radiant exposure (Documenta Geigy Scientific Tables, 1970; p. 85).

Table 2 Summary of incidence of adverse photosensitivity reactions and calculation of photosensitivity indices (PI)

Drug	Radiant exposure H (Jcm^{-2})	Number of adverse responses	Number of patients phototested	% Probability (95% confidence interval in parentheses)	PI (kJ)
Benoxaprofen	0.2	1	7	14.3 (0.4–58)	12
	0.5	2	7	28.6 (3.7–71)	30
	0.7	3	7	42.9 (9.9–82)	42
	1.0	6	7	85.7 (42–99)	60
	1.4	7	7	100 (59–100)	84
Ibuprofen	< 4	0	2	0 (0–84)	0
Indomethacin	< 4	0	3	0 (0–71)	5.3
Ketoprofen	< 4	0	1	0 (0–100)	1.4
Naproxen	1.4	1	6	16.7 (0.4–64)	8.2
	4	3	6	50 (12–88)	23
Piroxicam	0.5	1	9	11.1 (0.3–48)	0.6
Tiaprofenic acid	2	1	9	11.1 (0.3–48)	20
	4	2	9	22.2 (2.8–60)	39

Figure 2 The absorption spectra of the NSAIDs studied here.

Furthermore, we may test the hypothesis that the response curve relating the probability of an adverse photosensitive reaction to the photosensitivity index is likely to be sigmoid in shape by plotting the data on probability graph paper. This is illustrated in Figure 3 where probit analysis (Finney, 1964) applied to the transformed data yields a correlation coefficient of 0.87.

This analysis may be extended to estimate the

photosensitivity reactions due to sunlight likely to be encountered by subjects taking NSAIDs. Equation 2 needs to be modified to take into account the range of wavelengths in the solar spectrum, such that

$$PI = M.F \int_{t_1}^{t_2} \int_{295 \text{ nm}}^{400 \text{ nm}} E(\lambda, t) \epsilon(\lambda) d\lambda dt \quad \text{Joules} \quad (3)$$

where F is the fraction of the maximum available solar

Figure 3 The response curve relating the probability of an adverse photosensitive reaction to the photosensitivity index.

○ benoxaprofen, ● naproxen, ■ piroxicam and ▼ tiaprofenic acid.

UVR that is actually received on the subjects' skin, t_1 and t_2 are the times of day at which sunlight exposure is commenced and ended respectively, $E(\lambda, t)$ is the spectral irradiance ($\text{Wcm}^{-2} \text{nm}^{-1}$) of solar UVR on a horizontal, unshaded surface at wavelength λ nm and time of day t , and $\epsilon(\lambda)$ is the extinction coefficient

($\text{cm}^2 \text{mg}^{-1}$) at wavelength λ nm for the appropriate drug (see Figure 2).

The lower limit of wavelength integration is taken as 295 nm since this is the approximate shortest wavelength present in terrestrial sunlight; the upper limit is taken as 400 nm since all drugs exhibit negligible absorption in the visible region of the spectrum, i.e. $\epsilon(\lambda) \approx 0$ for $\lambda > 400$ nm.

The exposure fraction F , can take any value from 0 to 1 corresponding to complete shielding from sunlight, to exposure on an unshaded horizontal surface. Measurements of personal solar UV doses received by people in different environments have been carried out by several workers (Challoner *et al.*, 1976; Leach *et al.*, 1978; Diffey *et al.*, 1982). The results of these investigations suggest that F is in the range 0.01 to 0.04 for people with essentially indoor occupations, such as office workers, around 0.2 for outdoor workers and pastimes such as sightseeing, rising to 0.8 for sunbathing on a beach.

A set of empirical equations based upon experimental measurements (Diffey, 1977) have been used to compute $E(\lambda, t)$.

Calculations of the photosensitivity index (PI) given in eqn. 3 have been carried out for a one hour exposure to midday summer sunshine in the UK, assuming an exposure fraction (F) of 0.2. By reference to Figure 3, it is possible to estimate the probability of photosensitive reactions for a given PI. These results are summarised in Table 3, together with the number of photosensitive reactions for each drug reported to the Committee on Safety of Medicines during the period 1964–81. It may be seen that, in general, the number of reported reactions for each drug increases with the photosensitivity index (and hence the predicted probability of a photosensitive reaction).

This simple model has demonstrated that in those cases of drug induced phototoxicity where the action spectrum *in vivo* and the absorption spectrum *in vitro* are similar, it may be possible to predict the incidence of photosensitivity by consideration of three factors:

Table 3 The predicted probability of a photosensitive reaction following 1 h exposure to midday summer sunlight in the UK compared with the number of reported photosensitive reactions

Drug	Photosensitivity index (kJ)	Predicted probability of photosensitive reaction (%)	* Number of reported photosensitive reactions 1964–81
Benoxaprofen	28	30	1072
Ibuprofen	~ 0	very small	6
Indomethacin	1.6	very small	3
Ketoprofen	0.2	very small	3
Naproxen	4	8	6
Piroxicam	2	7	12
Tiaprofenic acid	6	9	Not available

* Data from Committee on Safety of Medicines (1982), personal communication

the mass of drug normally ingested; the spectral absorption characteristics of the drug; and the quantity and spectral quality of the radiation (e.g. sunlight) to which the patient may be exposed. It remains to be seen whether the method is applicable to more rigorous studies on other groups of phototoxic drugs.

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(Received April 18, 1983,
accepted August 15, 1983)