# Drug Photosensitivity in Norway

*Sir,*

The registration of unwanted side effects during drug therapy was initiated by the WHO at the end of the 1960's as a consequence of the severe teratogeny due to thalidomid (1). In Norway, the Department of Health appointed The Adverse Drug Reaction Committee to manage and administer the data. The first registrations started in 1970.

Clinical photosensitization due to systemic drugs is mainly caused by a handful of pharmacological substances: the sulphonamides and their derivatives, tetracyclines, phenothiazines and non-steroidal antiinflammatory drugs (NSAIDs) (2). Theoretically, any drug capable of absorbing light may induce phototoxic effects, provided that the excitation energy is not dissipated in heat. Photoallergic reactions require specific mechanisms by means of a delayed contact allergy.

We have reviewed the number of photosensitivity reactions reported as unwanted side-effects during drug therapy from 1970 to 1993 and discuss the results related to actual prescriptions of the drugs used in the same time period (3).

Computerized data on unwanted side-effects were obtained from the Norwegian Medicines Control Authority. The total number of side-effects was compared to the total number of unwanted side-effects concerning the skin and appendages and especially the number of photosensitivity reactions.

From 1970 to 1993, 13,000 unwanted side-effects were registered by the Adverse Drug Reaction Committee. NSAIDs, tetracyclines, benzodiazepines, phenothiazines, fungicides, nalidixic acid, quinidine, amiodarone, quinolones, antihistamines, sulphonamides, diuretics and antidiabetics accounted for 3,879 of the registered side-effects. Out of these, 776 (20,0%) involved the skin and appendages. Forty-one out of 776 (5,3%) skin reactions were classified as photosensitivity reactions (Table I). The photosensitivity reactions were due to a limited number of drugs within the different pharmacological groups (Table II).

Table I. *Number of unwanted side-effects reported in the time period 1971–1993 (the quinolones* have been reported since 1985), with special reference to skin and photosensitivity reactions*

| Pharmacological group | Reported side-effects | Skin reactions | Photosensitivity reactions |
|---|---|---|---|
| NSAIDs | 1459 | 186 | 5 |
| Tetracyclines | 195 | 63 | 12 |
| Benzodiazepines | 151 | 17 | 0 |
| Phenothiazines | 264 | 16 | 1 |
| Fungicides | 14 | 2 | 0 |
| Nalidixic acid | 53 | 7 | 2 |
| Quinidine | 76 | 10 | 2 |
| Amiodarone | 33 | 4 | 2 |
| Antihistamines | 249 | 47 | 5 |
| Quinolones* | 19 | 8 | 0 |
| Sulphonamide (+combinations) | 890 | 318 | 1 |
| Oral antidiabetics | 64 | 8 | 1 |
| Diuretics | 412 | 90 | 10 |
| Σ | 3879 | 776 | 41 |

Table II. *Drugs from the different pharmacological groups which induced photosensitivity reactions*

| Pharmacological group | Drug | Number of photosensitivity reports |
|---|---|---|
| NSAID's | Piroxicam | 3 |
| | Ketoprofen | 1 |
| | Sulindac | 1 |
| Tetracyclines | Doxycycline | 7 |
| | Tetracycline | 3 |
| | Lymecycline | 1 |
| | Demethylchlortetracycline | 1 |
| Phenothiazines | Trifluoperazine | 1 |
| Nalidixic acid | Nalidixic acid | 2 |
| Quinidine | Quinidine | 2 |
| Amiodarone | Amiodarone | 2 |
| Sulphonamides | Sulphamethoxazole | 1 |
| Oral antidiabetics | Chlorpropamide | 1 |
| Diuretics | Hydrochlorothiazide | 9 |
| | Furosemide | 1 |
| Antihistamines | Terfenadine | 5 |
| Σ | | 41 |

## DISCUSSION

Although photosensitivity is a well-known problem, there is not much data on the actual risk for photosensitization during drug therapy. During a 7-year period, from 1964 to 1971, 454 photosensitivity side-effects were reported to the British "UK Committee on Safety of Medicine" (4). Protriptylin, demethylchlortetracycline and nalidixic acid were among the most frequent drugs inducing photosensitivity. Compared to the overall prescriptions in the same time period, one photosensitization was likely to occur in about every 200,000th prescription (4). Data from Sweden in the time period 1972 to 1983 show similar results, except that protriptylin was uncommon in inducing photosensitive reactions (2). In Finland, 464 adverse drug reactions were reported in the time period 1966 to 1970. Out of these, 187 reports were due to sulphonamides, and 9 reports were due to photosensitivity (5). Since 1981, the NSAIDs are among the drugs causing the most frequent photosensitivity reactions. Benoxaprofen induced photosensitivity in about 50% of all prescriptions and had to be withdrawn from the market (6). In our study, the tetracyclines, diuretics and NSAIDs were among the drugs most frequently inducing photosensitizing adverse drug reactions.

Aside from the varying phototoxic potency of different drugs, other factors may influence the intensity of adverse skin reactions. In a study testing 22 persons on the diuretic bendroflumethiazide, a lowered minimal erythema dose (MED) in the UVA range in 13 of the test persons was found (7). The MED was still in the range of normal, but the authors suggested that a lowered minimal erythema dose is the first step to induce clinical photosensitivity.

The estimation of the actual risk is a difficult task. In the British study (4), over 100 million tablets were prescibed in the time period, whereas in Norway, with about 4 million inhabitants, there is an expected risk for photosensitivity

reactions, in approximately 1 in 6 million prescriptions of NSAIDs and 1 in 5 million prescriptions of diuretics (3). These numbers are below the incidence rates from the U.K. and may be due to a lower sunlight exposure. Another factor influencing the data is the number of adverse reactions reported. The Adverse Drug Reaction Committee encourages medical doctors to report all adverse drug reactions; severe reactions have to be reported. Disadvantages may be that known photosensitizers are not reported when a photosensitivity reaction is suspected, and that confirming procedures, such as phototesting in dermatological departments, are not routinely applied. The reports are supplied by all kinds of medical specialities, and uncertain cases will affect the overall conclusions.

Nevertheless, reporting systems on unwanted side-effects during drug therapy are useful and necessary to detect harmful reactions, and as no predictive testing detects all photosensitizers, reporting systems are of great value in establishing and analyzing data on unwanted drug reactions.

## REFERENCES

1. Venulet J. The WHO drug monitoring programme: the informative years (1968–1975). In: Drug surveillance: international cooperation past, present and future. Proceedings of the XXVIIth CIOMS Conference, Geneva, Switzerland 14–15. September 1993: 13–19.
2. Ljunggren B, Bjellerup M. Systemic drug photosensitivity. Photodermatol 1986; 3: 26–35.
3. Legemiddelforbruket i Norge 1988–1992. Norsk Medisinaldepot AS, Oslo 1993.
4. Magnus IA. Dermatological photobiology. Oxford: Blackwell Scientific Publications, 1976.
5. Kuokkanen K. Drug eruptions. Acta Allergol 1972; 27: 407–438.
6. Halsey JP, Cardoe N. Benoxaprofen: side-effect profile in 300 patients. BMJ 1982; 284: 1365–1369.
7. Diffey BL, Langtry J. Phototoxic potential of thiazide diuretics in normal subjects. Arch Dermatol 1989; 125: 1355–1358.

*Accepted March 14, 1996.*

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