MEYLER'S SIDE EFFECTS OF DRUGS

A SURVEY OF UNWANTED EFFECTS OF DRUGS REPORTED IN 1972–1975

VOLUME VIII

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Leopold Meyler

Professor Leopold Meyler, the founder of this series, died on 19th September, 1973, while on holiday in the South of France. He had completed Volume VII and had already begun to make arrangements for the production of Volume VIII. He was a remarkable man, as is evident from his career. At an age when others retire he joined our department and became the first professor of clinical pharmacology in Groningen, so introducing this discipline into The Netherlands. His appointment to the chair was a belated recognition of his work. He was one of the first to realize that drugs could be the cause of unexplained diseases. This idea has now become commonplace and it is difficult to recall that 20 years ago few people considered it. Meyler contributed greatly to this change in attitude.

His interest in side effects began while he had pulmonary tuberculosis and was in a sanatorium being treated with drugs that included para-amino-salicylic acid. He developed a high fever, for no apparent reason. After PAS had been considered as a possible cause, and discontinued, the fever ceased, and Meyler felt strongly that all physicians using this drug should be able to find out that this drug could cause high fever. The same idea was of course applicable to all drugs, and Meyler therefore began to collect all the reports on side effects he could find; this resulted in the first volume of "Side Effects". He also produced another important and successful series on "Drug-Induced Diseases". As a result of these activities some inevitably regarded Meyler as an "anti-drug man", but this was unjust. He wanted to encourage the well-considered and purposeful use of drugs, and fought wholeheartedly against their misuse. He achieved a great deal, and the medical profession has much to thank him for.

All this might suggest that Meyler was a somewhat cool and remote compiler of books, but nothing would be further from the truth. He was a fiery man who passionately sought to get ideas accepted. Such a man inevitably antagonizes some people, and to these he seemed at times excessively demanding. However, he made greater demands on himself than on anyone else. He was never self-centred, and above all he wanted the best done for his patients and for his students. He taught with enthusiasm and the students enjoyed his courses. But through his books his influence on medicine became international and they are a lasting monument to his vision and industry.

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how to use this book

When Professor Leo Meyler died in September 1973, the foundations for the present edition of his *Side Effects of Drugs* had to a large extent already been laid. In its final form, the present volume continues the tradition set by its predecessors, but it also incorporates some new elements, the need for which has become evident in practice.

The fact that information on the undesirable effects of medicines is increasing so fast, and that information needs differ so widely, naturally raises the question as to whether these needs can in fact be met by books at all. Might a universally accessible computer system of drug information not be more effective? The answer, surely, is that data systems are likely to an increasing extent to complement books such as this one, but are very unlikely to replace them. It will be a long time before every drug prescriber has ready access to a computer terminal and even longer until such channels provide him with all the detailed and often conflicting material which he may need to form his own judgement. That is the basic problem of drug information: the most important material is often that relating to matters which are still nascent, disputed, or poorly quantified. Each section of *Side Effects of Drugs* therefore opens with a review of well-established facts (the detailed evidence for which is to be found in earlier volumes in the series) and then proceeds to analyze recent literature which may add to or modify earlier knowledge. Some of these recent papers justify firm conclusions; many others provide only pointers, and in reviewing them one can do little more than suggest how they might be interpreted.

Since the summaries provided in this book will not be sufficient for every need, the system of literature references has been modified, so as to indicate whether or not the reader is likely to find substantially more information by consulting the original publication. The following code has now been introduced into most chapters:

R: In the original paper, the point is *reviewed* in some detail with reference to other literature.

r: The original paper *refers* only briefly to the point, on the basis of evidence adduced by other writers.

C: The original paper presents detailed *original clinical evidence* on this point.

c: The original paper provides *clinical evidence*, but only briefly.

The code has not been applied to animal pharmacological papers and has not been employed for older literature dealt with in earlier volumes. In order to keep this volume within manageable proportions, both for its readers and its writers, closely related drugs with similar side effects (e.g. the phenothiazines) have commonly been dealt with as a group. The discussion on single drugs in the group is limited to those matters on which an individual preparation differs from the general pattern either quantitatively or qualitatively.

The structure of the book as a whole and of the indexes reflect the fact that, in most situations in which this book is used, it is possible (and most

convenient) to search for information under the name of a particular drug or group of drugs. It is hardly possible to devise a full index classified according to side effects, since a particular effect may be caused by hundreds of different compounds; however, primary entries have been provided in a separate index for a large number of side effects. In making the inevitable selection, preference has been given to those side effects which are acute or life-threatening, those which are discussed in some detail in the present volume, and those which are unexpected. Before assuming that a given drug has not been reported to have a particular side effect, however, the reader should always consult the relevant chapter.

Both the Index of Drugs and the Index of Side Effects have been compiled by Dr. H. Kettner, Middelburg Hospital, Middelburg.

Drug products are in general dealt with in the text under their most usual non-proprietary names; where these are not available, chemical names have been used; fixed combinations usually have no non-proprietary connotation and here trade names have been used as necessary. The most common synonyms, including the more usual trade names, can be found in the Index of Synonyms.

Not all the developments planned for these volumes could be brought to fruition in this edition, and in some chapters a special approach to the material has proved necessary because of the nature of the problems. From 1976 onwards a series of yearly publications is envisaged which will serve to complement "Meyler's Side Effects of Drugs" by providing up-to-date information on current developments in this field.

Since the publication of Volume VII, the accessibility of recent information on side effects has been greatly improved by the establishment in many more countries than hitherto of Adverse Reactions Bureaux, where information from physicians on suspected side effects is recorded, analyzed, and insofar as possible made available. The physician who is in need of the most recent and still unpublished data on any issue would do well to consult his national Adverse Reactions Bureau. Addresses are available from the World Health Organization, International Drug Monitoring System, Geneva, Switzerland.

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contents

P. H. Connell

1 central nervous system stimulants

ANALEPTICS

AMINOPHYLLINE

Intoxication has been described, especially in young children. It can occur after a single suppository, though the toxic dose has usually been much greater. Idiosyncrasy may play a role in some such incidents. More commonly, however, overdosage is responsible. The dose administered to a child should not exceed 5 mg/kg body weight by mouth or 7 mg/kg by rectum. Either may be repeated after 6–8 hours. The effect is cumulative and the danger of overdosage is compounded if the drug is given repeatedly (1[C]).

Cases of poisoning often go unrecognized in the early stages. The following symptoms have been reported: nausea, vomiting (sometimes with haematemesis), vertigo, insomnia, restlessness, anxiety, agitation, confusion, delirium and convulsions, coma, pyrexia, respiratory paralysis, dehydration and shock. Associated minor effects reported include proteinuria, headache and disorders of vision. If the condition is recognized early and the drug discontinued immediately, recovery may be rapid and only supportive treatment will then be needed (SED VI, 1).

Probably symptoms of overdosage are not always recognized as such and may well be attributed to the disorder (e.g. asthma) for which a theophylline preparation has been prescribed (2[C]). Individual case reports in children include a 4.5-year-old boy who nearly died after being given 60 mg/kg body weight in 2 hours, and a 1-year-old child who received rectally 2 suppositories containing 700 mg aminophylline (3[C]).

In adults, the commonest side effect is nausea. Adequate dosage by mouth is often impossible on acount of this. Gastrointestinal irritation has also been reported after the use of suppositories and intravenous administration (4[R]). Intravenous administration may cause palpitations, dizziness, irritability, hyperventilation, nausea and vomiting. Vascular collapse and even death may follow rapid administration (5[R]).

A recent report described a 4-year-old child weighing 17 kg and given 500 mg aminophylline intramuscularly followed by 250 mg every 6 hours by mistake for ampicillin; the child showed severe toxic symptoms 10 hours later. Two brief episodes of mental confusion and hallucinations occurred (7[CR]).

A report of a 12-year-old asthmatic who developed an urticarial reaction associated with generalized pruritus following the intravenous administration of aminophylline notes that a fortuitous challenge with a second dose of the drug produced an identical clinical reaction. The immunogenic nature of the reaction was studied (8[CR]).

The occurrence of 1:1 conduction in atrial flutter after intravenous injection of 300 mg of aminophylline has been reported in a cyanotic 71-year-old woman admitted to hospital because of acute pulmonary oedema (9[C]).

The administration of a therapeutic dose of aminophylline to a 55-year-old woman was followed by development of thrombocytopenia and haemorrhagic diathesis. The immunological character of these changes was confirmed with serological investigations (10[C]).

A report of 3 patients, 2 men of 72 years, and one a woman of 73, given aminophylline, draws attention to the possibility that a true clinical sensitivity to aminophylline may aggravate the asthma for which they are given the drug, and notes that in 2 of the patients the dyes contained in the drug preparation may be responsible (11[C]).

A double-blind study to investigate the therapeutic effectiveness of Entair A capsules (theophylline and guaiphenesin), with Entair without the addition of 20 mg ephedrine hydrochloride, in asthmatic and chronic bronchitic patients, noted that side effects occurred in one-third of the group in the study. These comprised nausea, vomiting and diarrhoea. Control of these was achieved easily with small doses of antihistamines (12[CR]).

The bronchodilator effectiveness and prevalence of untoward effects of orally administered single doses of aminophylline (500 mg) and dihydroxypropyl theophylline (DHTP) (500 mg and 1,000 mg) were com-

Table 1. *Side effects reported during study (13C)*

	Number reporting side effects	Side effects (number)
Placebo	2	Weakness (1) Abdominal pain (1) Shakiness (1)
DHPT 500	2	Nausea (1) Drowsiness (1) Rash (1) Headache (1)
DHPT 1,000	2	Nausea (1) Dyspnoea (1)
Aminophylline 500	8	Nervousness (3) Nausea (2) Vomiting (1) Dizziness (2) Palpitations (1)

pared in subjects with partially reversible airway obstruction in a double-blind cross-over design. Twelve subjects were studied. The side effects are shown in Table 1. It is suggested that 500 mg aminophylline may have been excessive and that adequate bronchodilation might have been achieved with a lower dose and fewer side effects (13C).

A controlled, clinical evaluation of a new oral aminophylline (Broncordil) involved a double-blind cross-over trial against a placebo in patients with a history of daily attacks of bronchospasm for at least 3 months. Nine patients out of the 40 studied showed side effects on aminophylline. Three had nausea and vomiting, 2 had indigestion and gastric upset, 1 had hyperacidity and a burning sensation in the stomach, 1 had loose motions, 1 had headache and 1 anorexia. These effects were regarded as mild (14CR).

Theophylline toxicity due to impaired theophylline degradation has been reported in a 72-year-old man with severe chronic obstructive pulmonary disease and normal liver function. He had convulsions at a time when his serum theophylline level was 86 μg/ml. The day before convulsing he had received 960 mg of theophylline (17.5 mg/kg). The serum level of theophylline declined with a half-time of approximately 28 hours. The patient was also markedly sensitive to the anticoagulant effects of warfarin. These findings, as the authors point out, mean that severe toxicity to theophylline may occur during administration of the ordinarily recommended dosage, and the need to measure serum theophylline levels is therefore stressed (15C).

AMIPHENAZOLE

The adverse effects reported are fairly similar to those of nikethamide. They comprise restlessness, muscular twitching, mental disorientation in the elderly, convulsions with large doses, coughing, prolonged and forced expiration, nausea and vomiting, sweating and skin irritation. The side effects are stated to be less distressing than those caused by nikethamide (16R).

Rashes and in one case a severe lichenoid eruption have been reported with the use of amiphenazole (17CR, 18C). Oral ulceration has also been reported in amiphenazole sensitivity. This case differed from other published cases in that the patient initially presented with severe ulceration of the mouth and was referred first to a dental practitioner and then by him to a dental hospital. The oral ulceration was lichenoid in character and the patient was a 53-year-old man who had been on amiphenazole for 2 months before he developed a sore mouth. The dose of amiphenazole was 100 mg q.d.s. and the patient was also receiving orciprenaline 20 mg q.d.s. (19C).

BEMEGRIDE

Reported symptoms of overdosage comprise muscular twitching (especially in the hands and face), convulsive spasm, abnormally brisk reflexes, hyperventilation, restlessness, euphoria, confusion, visual hallucinations, vomiting and retching, and a tendency to hypotension (20R).

CAFFEINE

Large doses may cause nausea, vomiting, diuresis, tachycardia, cardiac arrhythmias (extrasystoles), insomnia, restlessness, nervousness, tinnitus, tremors and scintillating scotomas. Even an average dose may cause nausea, nervousness, insomnia, and increased diuresis. A review of factors affecting caffeine toxicity (21R) notes that little is known about the lethal dose of caffeine in human subjects and that fatal poisoning is extremely rare. Death has been reported in a case after intravenous administration of some 3.2 g of caffeine, or about 57 mg/kg body weight, and in one human subject con-

vulsions followed the intravenous injection of 400 mg or about 7 mg/kg body weight (22^{C}).

It has been noted that absorption of caffeine after oral administration is faster than after intramuscular administration. It is also suggested that some deaths following oral caffeine may be due to cardiovascular shock from severe gastroenteritis which may occur in animals. Extrapolation of findings from animal studies suggests that chronic toxicity to caffeine is not likely to occur in man since some 60–100 cups of coffee per day would be required to produce chronic toxic effects in healthy persons (21^{R}). However, a recent review (23^{R}) covering the historical background and present position in general terms, notes that the average cup of percolated coffee is believed to contain 100–150 mg of caffeine. A cup of tea contains as much as 110 mg caffeine, though 50–75 mg is a more typical amount, together with theophylline. Instant coffee contains smaller amounts (70 mg per cup). Many soft drinks, such as "cola" drinks, also contain substantial amounts of caffeine.

Nearly 28% of the Ontario adult population drinks the caffeine equivalent of 5 or more cups of coffee each day in the form of either tea or coffee, and this level of intake is similar to that for Canada as a whole. Studies at Stanford University, California, in the 1960's had indicated that caffeine both prevented and disturbed sleep and elevated mood but not performance. These studies also noted characteristic dysphoric symptoms such as irritability, inability to work effectively, nervousness, restlessness, lethargy and headache when caffeine was taken by non-users, or was not taken by regular users. Thus a withdrawal syndrome is postulated and thought to probably affect as many as a million Ontario adults who are therefore drug-dependent. It is suggested that caffeine-induced sleeplessness, irritability and relative ineffectiveness may lead to the use of tranquillizers to combat these effects. Furthermore, the use of caffeine by hyperkinetic children may lead to adult dependence later.

It has further been reported recently that a high intake of caffeine can produce symptoms that are indistinguishable from those of anxiety neurosis such as irritability, tremulousness, occasional muscle twitchings, insomnia, sensory disturbances, tachypnoea, palpitations, flushing, arrhythmias, diuresis and gastrointestinal disturbances, and that the caffeine withdrawal syndrome and the headache associated with it may also mimic anxiety. A failure to respond to psychopharmacological agents should alert the physician to the possibility of caffeinism (24^{CR}).

Caffeine is a potent and prolonged stimulant of hydrochloric acid secretion in the duodenal ulcer patient. The consumption of inordinate quantities of caffeine-containing Cola beverages has been incriminated in the perforation of a duodenal ulcer in man.

Allergy

A review of the chemistry of atopic allergens has drawn attention to the observation that workers in the coffee industry not infrequently develop bronchial asthma, rhinitis or dermatitis on exposure to the dust filling the air in the factory during the process of stripping the chaff from the raw bean prior to roasting. These people often present positive immediate-type reactions upon intradermal administration of extracts of green coffee chaff and green coffee bean. The significance of chlorogenic acid in this context is still debated, and some investigators note that roasted coffee is not allergenic to man (25^{R}).

Cardiovascular

A consistent finding in the Boston Collaborative Drug Surveillance Program has been that patients discharged from hospital with a diagnosis of acute myocardial infarction drink more coffee on average than do patients discharged without that diagnosis (26^{CR}). A discussion of this report which notes that there was no significant difference in the quantity of tea ingested between the 2 groups recommends that the possible role of coffee drinking in the aetiology of acute myocardial infarction requires re-evaluation (27^{R}). Further comment on the use of international comparisons and the need for a large prospective clinical trial designed to study coffee consumption as a risk factor in the pathogenesis of atherosclerosis has been made (28^{R}).

Metabolic effects

Relatively little is known about the direct effect of coffee and caffeinated beverages on blood cholesterol. A study has shown that coffee or equivalent amounts of caffeine administered intramuscularly produce an in-

crease in free fatty acids (FFA). The increase in FFA produced by caffeine is similar to, but much more prolonged than, that produced by nicotine. These alterations may be a result of a stress effect produced by caffeine. Many observers have shown that an increase in FFA predisposes to a rise in lipoprotein lipids, including an increase in blood cholesterol (29[C R]). Hyperglycaemic effects in man have been reported (30[C R]).

Mutagenic activity

A study of tissue culture cells, mainly HeLa cells (which proved to be the best available material for studying induced chromosome breakage in human cells), and later leukocytes under the influence of varying concentrations of caffeine, suggests that, assuming caffeine is equally mutagenic in human testicular tissue, the amount of damage (breakage) would be in the neighbourhood of the "natural mutation rate" (31[C R]).

A recent review of caffeine as a teratogen and mutagen in animals contains tabulated data. This suggests little teratogenic danger to man and observes that man may be protected by his rapid metabolism of caffeine, only 1% being excreted unchanged. Two reports of studies in which caffeine was added to human lymphocytic cultures noted delayed mitosis and excessive chromatid breaks but there were no reports of chromosomal studies of cells from heavy caffeine users (32[R]).

A study of human lymphocytes in 17 different healthy donors investigated the randomness of chromosomal aberrations and noted that the amount of damage in chromosomes No. 3 and No. 16 was two times or greater than expected. The relevance of exposure to chemicals such as caffeine and viruses related to the Rous sarcoma virus is discussed (33[C]). In an attempt to determine the mechanism of action of caffeine clastogenicity (chromosome breakage), substances directly or indirectly affecting the synthesis or integrity of DNA were added to caffeine-treated human lymphocyte cultures. At concentrations of 250–750 μg caffeine per ml, no evidence could be found which would indicate that caffeine was acting as a purine analogue, inhibitor of phosphodiesterase, stimulator of adenylosuccinate (S-AMP) lyase, labilizer of lysosomes, or as a clastogen which could be inhibited by an antimutagen (34[C R]).

Kidneys

The administration of caffeine citrate daily moderately increased the mean urinary renal excretion rate of tubular cells and red blood cells in 10 volunteers (35[C]).

Psychosis

A case of "caffeine psychosis" in which fighting, kicking and biting occurred has been reported (36[C]).

DOXAPRAM

This drug, introduced in 1965 as a new analeptic agent, is similar in its actions to other non-specific central stimulants. Like all analeptic drugs it may cause generalized stimulation of the nervous system, particularly if large doses are given. Thus, hyperactivity, muscle twitching, increased deep tendon reflexes, laryngospasm, tachycardia, and elevation of blood pressure may occur. Doxapram is contraindicated in the presence of epilepsy or other convulsive disorders, hypertension, cerebral oedema, hyperthyroidism and phaeochromocytoma and should be used cautiously, if at all, in patients receiving sympathicomimetic agents or monoamine oxidase inhibitors because it augments sympathetic activity (37[R]).

In a series of 29 patients anaesthetized with conventional anaesthetic agents and techniques, 9 showed ECG arrhythmias, but in only 5 instances were the arrhythmias associated primarily with analeptic administration. Moreover, the arrhythmias which followed the doxapram injection were not considered serious: in 2 instances they consisted of a single premature ventricular contraction, and on 3 occasions they consisted of multiple ventricular extrasystoles which were self-limited and lasted for not more than 3 minutes (38[C]).

A study of 285 male and female surgical patients, ranging in age from 2-84 years with 206 (71%) falling between 21 and 60 years of age, reports that respiratory stimulation occurs safely and predictably at doses far below that required to elicit generalized central nervous system stimulation. Small, frequently repeated doses permitted better control and prevented undue stimulation. Side effects included transient neuromuscular signs of excessive central nervous system stimulation at single dose levels of 1 mg/kg in a very few patients. Seven patients exhibited excitement, tremor was evident in 3, and rigidity in 2. Decreasing the dose by half

gave more predictable and desirable responses in these instances. Possible side effects related to the direct action of the drug, or to physiological responses to the drug's action, included coughing, laryngospasm, breath-holding and salivation. Coughing and gagging were considered to be probable manifestations of the return of protective reflexes secondary to arousal (39[C]). A study of 12 patients receiving intravenous drip infusion of doxapram by the double-blind method noted excitement in 3 cases (40[C]). A study of 10 patients receiving intravenous infusion of doxapram noted that the mean pulmonary arterial pressure was significantly increased but that in the majority of patients the pulmonary hypertension remained discrete and was more than compensated by the favourable effects of doxapram on gas exchanges (41[C]).

ETAMIVAN

The incidence of side effects when the drug is administered intravenously has been stated to be fairly high (42[C]). Sneezing, laryngospasm and substernal chest pain have been recorded, as well as muscular twitching (especially in the face), sometimes heralding generalized convulsions, when the infusion is too rapid or the dose too high. Etamivan is contraindicated in the presence of known or suspected epilepsy and in patients receiving monoamine oxidase inhibitors (43[R]).

FLUROTHYL

Flurothyl, a hexafluorinated ether, has been used as a therapeutic convulsant in psychiatry. It is not flammable or explosive under clinical conditions but its use as an intravenous convulsant in man has been temporarily discontinued because the carbowax in which flurothyl was dissolved contained polyethylene glycol, which can cause renal damage (44[C]). Its use as an inhalation convulsive agent has continued. Atropine and an ultrashort-acting barbiturate anaesthetic are usually given as premedication. One report notes that it is also compatible with propanidid, diazepam and halothane, but that the latter 2 drugs call for higher flurothyl dosage (44[C]).

A study of 16 patients treated alternately with flurothyl and ECT (15 suffering from depressive illness and 1 from schizophrenia) noted a variety of unwanted effects (Table 2). This study (45[C]) also noted that although the high-dose regimen produced a larger rise of systolic blood pressure than ECT the low-dose regimen (0.5 ml doses) did not show this difference. Some patients on low doses tended to show prolonged muscular twitching, and occasionally very quick awakening. Two patients had a sore throat for several days after treatment and 2 other patients showed intermittent jerking movements of the limbs up to 30 minutes after treatment. One patient in the large dose series had a recurrence of a fit 5 minutes after the first fit.

Table 2. *Unwanted effects of flurothyl (45[C])*

	Number of treatments		
	High dose 32	Low dose 20	Electric convulsive therapy (ECT) 44
Early effects			
Restlessness	6	2	0
Confusion	6	2	0
Dysphasia	4	0	0
Headache	4	1	1
Dizziness	1	1	1
Vomiting	2	0	0
Unreality	3	0	1
Others	2	0	0
Late effects			
Dysmnesia	5	3	5
Headache	1	3	2
Others	0	1	0

Serious unwanted effects were noted in the same study (45[C]). Three patients were very restless and required further thiopentone to control them. One patient had several runs of jerky movements, each lasting about 15 seconds, and 4 patients were severely disturbed, being confused, disorientated, unintelligibly dysphasic and resisting violently any attempt at interference. The most alarming reaction was a 5-minute fit following 3 ml flurothyl, after which the patient was restless, confused, disorientated, dysphasic, salivating and grinding his teeth. He remained like this for 3 hours and on admission to the ward his temperature was 37.4°C with neck stiffness and epigastric tenderness. Lumbar puncture was normal and he settled after 24 hours. None of these reactions, however, appeared to be directly related to the dose of flurothyl. The authors note that in general the clinical improvement was similar, but that there was a higher incidence of unwanted effects after a high