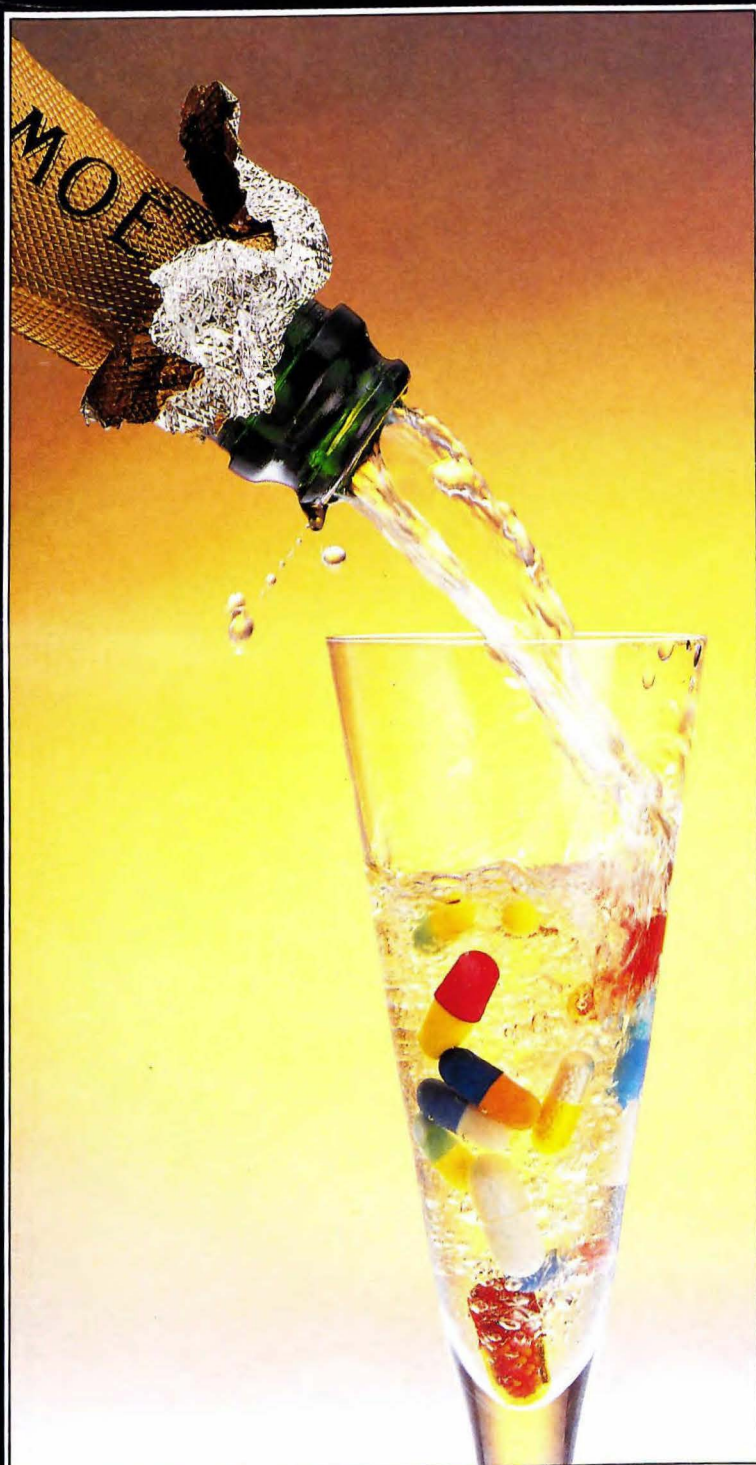


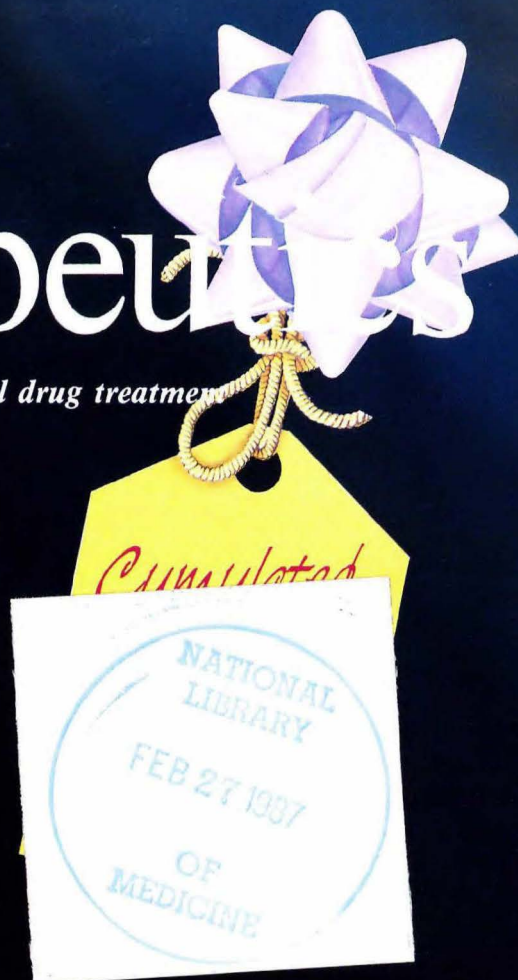
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Current Therapeutics

Australia's journal of practical drug treatment



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Christmas Feature
Drugs and Alcohol
Their Interactions and How to Avoid Them

Fixed Drug Combinations
Which Ones Can Be Recommended?

Therapeutic Use of Vitamin B₁₂, Iron and Folate

Constipation in Adults

Infections in Bones and Joints
Part II. Infectious Arthritis

December 1986
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Fixed Drug Combinations Which Ones Can be Recommended?

The view of drug regulatory bodies in Australasia is that fixed combination preparations are rarely necessary; sales figures, however, suggest they are extremely popular with patients and doctors alike. Only a limited number have been available until now but the scene is set for the possible introduction of many more. Doctors, therefore, should be aware of the potential advantages and disadvantages

G.M. Shenfield (Sydney)

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PRACTICAL THERAPEUTICS

Drugs and Alcohol Their Interactions and How to Avoid Them

Because alcohol is consumed on such a grand scale, in numerical terms, interactions between drugs and alcohol are important. This article discusses interactions that are particularly hazardous, especially those involving drugs in everyday use, and gives practical recommendations on how to avoid them

J.B. Saunders (Camperdown, NSW)

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Current Therapeutics

AUSTRALIA'S JOURNAL OF PRACTICAL DRUG TREATMENT



PRACTICAL THERAPEUTICS continued

Therapeutic Uses of Vitamin B₁₂, Iron and Folate

Because the haematinics, iron, vitamin B₁₂ and folate, should only be used when a specific deficiency exists, it is imperative that the precise deficiency is determined and the cause diagnosed. Once an accurate diagnosis has been made, as outlined in this article, definitive treatment of the cause and replacement of the deficient haematinic is appropriate

G.N. Brodie (Melbourne)

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Constipation in Adults

Constipation is a frequent symptom in Western communities and a wide range of therapeutic agents is available to treat it. Before prescribing laxatives, however, it is important that the general practitioner excludes or corrects any underlying pathology and pays attention to factors such as diet, exercise and development of regular bowel habits, as this may be all that is required

P.R.H. Barnes (Sydney)

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Infections in Bones and Joints

Part II. Infectious Arthritis

Septic arthritis is a relatively common medical emergency which may result in permanent joint damage unless treatment is initiated within 1 to 2 days. This part of the article discusses the microbiology and antibiotic therapy which has virtually eliminated mortality caused by infectious arthritis

A.S. Dickie (Auckland)

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Erratum

Current Therapeutics, Vol. 27, No. 11 (November 1986): In the new product entry for Natrilix Tablets on page 152 it should be noted that it was incorrectly stated that asthma is a side effect of this product. This should have read 'Other side effects include *asthenia*, headache, dizziness, vertigo and muscle cramps'.

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Gillian M. Shenfield

Department of Clinical Pharmacology, Royal North Shore Hospital, St. Leonards, NSW

Fixed Drug Combinations

Which Ones Can Be Recommended?

A combination should only be prescribed if each component is known to be necessary for the desired therapeutic effect. In addition the advantages of using a combination rather than a single drug should outweigh the added risks of using 2 or more drugs

Most patients on long term treatment with therapeutic drugs usually take more than one item. The more individual tablets that are prescribed, the greater the potential problems of compliance and of lack of control of the underlying condition. Intuitively it seems obvious that it would be more difficult to remember to take 2 tablets than to take 1, or to take 10 than to take 5. It is therefore tempting to consider the use of fixed combination preparations which contain 2 or more drugs in one formulation. This would reduce the number of doses to be taken and, hopefully, reduce the number missed.

However, the situation is not that simple and there are clearly very different opinions held by everyone who considers the problem. At the extremes are the regulatory authorities and the pharmaceutical manufacturers. There are about 1000 fixed combination

preparations listed in Mims but, excluding oral contraceptive preparations, insulins, topical agents and antacids, there are under 20 fixed combination tablets available on pharmaceutical benefits. This regulatory control is in keeping with the WHO list of 'essential' drugs which includes only 7 drug combinations; less than 3% of the total [1]. Thus, the view of drug regulatory bodies is that fixed combination preparations are rarely necessary. On the other hand, sales figures suggest that they are extremely popular with both doctors and patients.

Potential Advantages of Fixed Drug Combinations

The potential advantages of using fixed drug combinations are listed in table I.

... Fixed Drug Combinations

Table I.
Potential advantages of fixed drug combinations

Improved compliance
Synergism
Enhanced efficacy
Reduced side effects
Increased safety
Decreased potential for abuse
Reduced cost

Improved Compliance

The most frequently quoted reason for using fixed combination products is improved compliance. It seems reasonable to assume that the greater convenience of a single tablet would increase compliance and this has been observed for prophylactic iron in pregnancy [2] and for psychiatric outpatient therapy [3]. However, in neither of these studies was there any observable difference in therapeutic outcome. A more recent study of combination tablets containing a β -blocker and a thiazide diuretic found that 75% of patients preferred to take 1 tablet daily (as opposed to 2) but that combining 2 drugs in a single tablet had no effect on compliance [4]. Overall it appears that the vital factor is not the number of tablets taken but the number of doses prescribed.

Synergism

A fixed ratio drug combination can always be justified if its therapeutic effect exceeds the total effects of its components given separately in the same doses. The best known example of this is co-trimoxazole where the 2 components interfere selectively with 2 successive steps in bacterial folate metabolism. However, synergy probably operates only rarely under the conditions in which the combination is used *in vivo* [5]. Combinations of the antimalarial pyrimethamine with dapsone or sulphadoxine also come into the category of good synergistic combinations provided they are used in appropriate geographical areas. Recently

a combination of amoxycillin and clavulanic acid (a β -lactamase inhibitor) has been introduced and this has a much wider spectrum of antimicrobial activity than amoxycillin alone. Other good examples are hard to find.

Enhanced Efficacy

In the absence of true synergy there may still be enhanced efficacy as illustrated by levodopa with peripheral decarboxylase inhibitors and combined oral contraceptive preparations. The use of probenecid to reduce renal excretion of penicillin also comes into this category but the combined preparation is not available in Australasia. A new antibiotic, imipenem, is very rapidly hydrolysed by a renal dehydropeptidase enzyme. This means that the drug is rendered inactive and it also appears to cause renal toxicity. The process can be blocked by cilastatin, an inhibitor of the renal enzyme. Cilastatin alone has no antibiotic activity and imipenem alone has very little antimicrobial effect, therefore they are always given in combination to enhance the action of imipenem. Apart from these examples it is hard to find good clinical trials providing evidence for increased efficacy of combinations. In particular, combination analgesics have not been shown to be better than their individual components when tested in controlled trials.

Reduction of Side Effects

Supporters of combination therapy suggest that it is safer to use combinations of drugs proven to be safe and effective together than to indulge in indiscriminate polypharmacy. This would be true if all appropriate tests of therapeutic effect and pharmacokinetic and pharmacodynamic interactions had been performed for all available combination drugs. Unfortunately this is not the case and it cannot be assumed that all of them are automatically 'safe' [6].

Decreased Potential for Abuse

Occasionally addictive drugs are used for relatively minor purposes and an example of this is the opioid antidiarrhoeal agent, diphenoxylate. To discourage deliberate abuse and overdose it is only marketed in a combined preparation which contains 0.025mg of

BREAKTHROUGH THERAPY FOR ALLERGIC RHINITIS.

THE FIRST NON-SEDATING
H₁ RECEPTOR ANTAGONIST

Merrell Dow

ZYRTEC[®]
terfenadine 60mg tablets
Going beyond the limits of
conventional allergy treatment

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THE FIRST NON-SEDATING H₁ RECEPTOR ANTAGONIST.

DOES NOT READILY CROSS THE BLOOD BRAIN BARRIER



APOTEX_AZFL 0061711

ACTS ONLY ON PERIPHERAL H₁ RECEPTORS AT THERAPEUTIC DOSES.

Unlike conventional antihistamines TELDANE or its metabolites do not cross the blood brain barrier at effective therapeutic doses in sufficient quantity to affect the CNS.

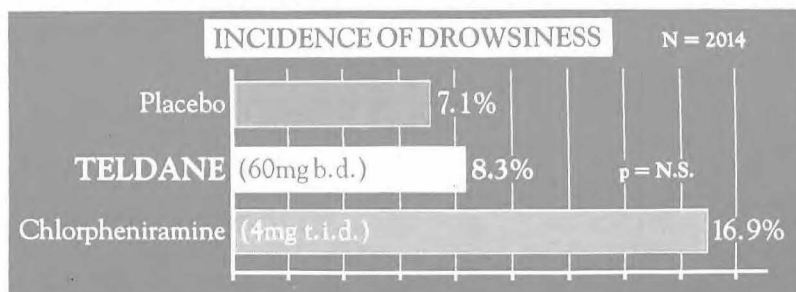
Hence TELDANE acts only on peripheral H₁ receptors.

The inability of TELDANE to cross the blood brain barrier has been confirmed by quantitative EEG.

"Terfenadine (TELDANE) failed to elicit the characteristic EEG or behavioural effects of sedative antihistaminics...."⁽¹⁾

NON-SEDATING. SEDATION EQUIVALENT TO PLACEBO.

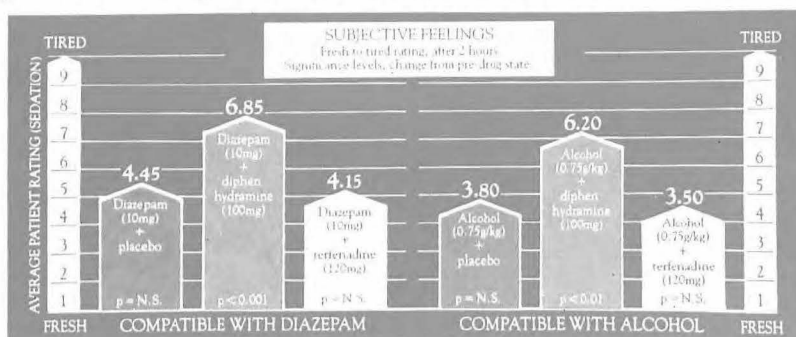
In double-blind, randomized, placebo-controlled studies involving 2,014 subjects, the reported incidence of sedation with TELDANE 60 mg b.d. did not differ significantly from that of placebo, while chlorpheniramine 4 mg t.i.d. produced twice the incidence.⁽²⁾



Studies of driving performance⁽³⁾ and co-ordination and reaction time^(4,5) confirm that the impairment of performance with TELDANE did not differ from placebo.

NO POTENTIATION OF SEDATIVE EFFECTS OF ALCOHOL OR BENZODIAZEPINES.

TELDANE was demonstrated to induce no potentiation of sedative effects of alcohol or diazepam in a comparative trial with diphenhydramine.⁽⁶⁾



Sedation-free relief of allergic rhinitis.

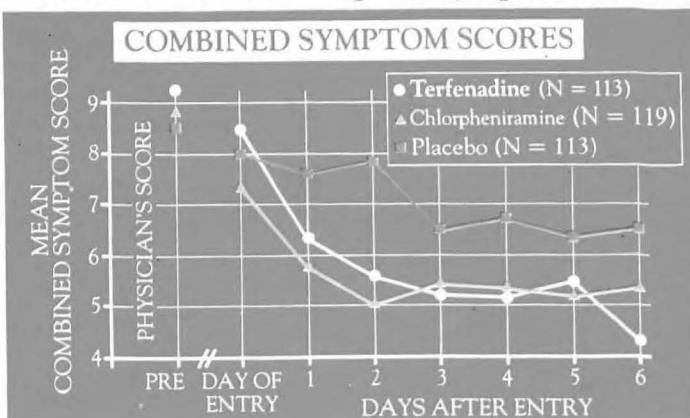
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EFFICACY EQUAL TO CONVENTIONAL THERAPY.

British and American studies comparing it with other treatments have shown that TELDANE is as effective as chlorpheniramine in relieving the symptoms of seasonal allergic rhinitis and conjunctivitis.^(7,8)

The combined symptom severity scores of seven allergy symptoms were rated during the treatment period by patients.

Symptoms included sneezing nasal congestion, rhinorrhea, red eyes, itchy nose/palate/throat, itchy eyes and watery eyes.



PROMPT ONSET OF ACTION AND INHERENTLY LONG ACTING.

TELDANE has a rapid onset of action and pharmacokinetic studies show it is inherently long acting.^(9,10) A 60 mg dose of TELDANE shows antihistaminic action for 12 hours or more. A simple b.d. 60mg tablet gives 24 hour relief of allergic rhinitis symptoms.

A FIRST FOR AUSTRALIA

TELDANE, the first non-sedating H₁ receptor antagonist available in Australia gives unmatched patient benefits:

Non-sedating.

Efficacy equal to conventional antihistamines.

Fast relief of symptoms.

No additive effects with alcohol or benzodiazepines.

Simple and convenient b.d. dosage.

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Merrell Dow

terfenadine

60mg tablets

Going beyond the limits of conventional allergy treatment

Merrell Dow Pharmaceuticals Australia Pty. Ltd. (Inc. in ACT)
100 Miller Street, North Sydney, NSW 2060

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APOTEX_AZFL 0061713

No matter how carefully you read this product information, you won't find the standard antihistamine drowsiness warning.

Prescribing Information — TELDANE (terfenadine) 60 mg tablets

Terfenadine is a histamine H_1 -receptor antagonist with the chemical name 1-(4-(1,1-dimethylethyl) phenyl)-4-(4-(hydroxydiphenylmethyl) piperidino) -butan-1-ol.

Terfenadine occurs as a white to off-white crystalline powder. It is freely soluble in chloroform, soluble in ethanol, and very slightly soluble in water.

PHARMACOLOGY: Terfenadine, a histamine H_1 -receptor blocking drug differs pharmacologically from conventional antihistamines regarding its effect on the CNS. Animal studies have demonstrated that at effective antihistaminic doses, terfenadine does not cross the blood-brain barrier in sufficient quantity to cause CNS effects. In clinical trials the reported frequency of drowsiness with terfenadine was similar to the incidence of drowsiness with placebo. EEG assessment in a limited number of healthy male volunteers have shown no depressant effect with single dose administration of 60 mg. In clinical trials the incidence of anticholinergic effects with terfenadine were similar to that with conventional antihistamines.

Histamine skin wheal studies in normal volunteers have shown that TELDANE in single and repeated doses of 60 mg has an antihistaminic effect beginning at 1-2 hours, reaching its maximum at 3-4 hours, and lasting for at least 8 hours after a single dose and for 12 hours after repeated doses.

Pharmacokinetic studies in healthy male subjects using ^{14}C -labelled terfenadine demonstrated that an oral dose of terfenadine is well absorbed from the gastrointestinal tract and rapidly and extensively biotransformed. Following administration of a single 60 mg TELDANE tablet detectable plasma levels were observed within one-half hour. Plasma levels peaked at about 2 hours after administration; a distribution half-life of 3-4 hours was followed by an elimination half-life of 20.3 hours. Terfenadine is extensively (97%) bound to human serum protein. Elimination studies with radiolabelled drug in male volunteers showed that fecal excretion accounted for 60% of the dose while 40% of the dose was eliminated via the urine. Almost all of the dose was eliminated in the form of metabolic products.

Following administration of single doses of 60 or 180 mg of TELDANE, a linear response was observed in maximum plasma concentration. Area under the curve (AUC) calculations, however, indicate a nearly four-fold increase in response for a three-fold increase in dose.

INDICATIONS: TELDANE is indicated for the symptomatic relief of acute seasonal allergic rhinitis in adults and children over 12 years of age.

CONTRAINDICATIONS: TELDANE is contraindicated in patients with a known hypersensitivity to terfenadine or any of its ingredients.

PRECAUTIONS: Consideration should be given to potential anticholinergic (drying) effects in patients with lower airway disease, including asthma.

USE IN PREGNANCY: Animal studies have shown no evidence of animal teratogenicity. Reproduction studies have been performed in rats at doses of 150 and 300 mg/kg/day and have revealed decreased pup weight gain and survival when terfenadine was administered throughout pregnancy and lactation. There are no adequate and well-controlled studies in pregnant women. TELDANE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN LACTATION: TELDANE is not recommended for nursing women. The drug has caused decreased pup weight gain and survival in rats given doses of 150 and 300 mg/kg/day throughout pregnancy and lactation. Effects on pups exposed to TELDANE only during lactation are not known, and there are no adequate and well-controlled studies in women during lactation.

PAEDIATRIC USE: Safety and effectiveness of TELDANE in children below the age of 12 years have not been established.

ADVERSE REACTIONS: Experience from clinical studies reported so far, including both controlled and uncontrolled

studies provides information on adverse experience incidence for periods of a few days up to six months (see table below). The usual dose in these studies was 60 mg twice daily, but in a small number of patients, the dose was as low as 20mg twice a day, or as high as 600mg daily.

In addition to the side effects reported in clinical trials (see table), adverse effects have been reported spontaneously during marketing of TELDANE that warrant listing as possibly associated with drug administration. These include: alopecia, anaphylaxis, angioedema, bronchospasm, depression, galactorrhea, insomnia, menstrual disorders (including dysmenorrhea), musculoskeletal pain, nightmares, palpitation, paresthesia, sweating, tachycardia, tremor, urinary frequency, visual disturbances and photosensitivity. In clinical trials, several instances of mild, or in one case, moderate transaminase elevations were seen in patients receiving TELDANE.

Mild elevations were also seen in placebo treated patients. Foreign marketing experiences include isolated reports of jaundice, cholestatic hepatitis and hepatitis: in most cases available information is incomplete. In neither the clinical trials nor foreign experience is a causal relationship of liver abnormalities to TELDANE use clear.

OVERDOSAGE: One case of overdosage has been reported in a 16 year old female who took 25 tablets (1500 mg). She was seen approximately one hour after ingestion and treated by gastric lavage. Her recovery was complete and uneventful except for a decrease in BP from 110/60 to 90/50 mm Hg two hours after admission.

Treatment of overdosage would reasonably consist of emesis (ipecac syrup), except in patients with impaired consciousness, followed by the administration of activated charcoal to absorb any remaining drug. If vomiting is unsuccessful, or contraindicated, gastric lavage should be performed with normal saline. Saline cathartics may also be of value for rapid dilution of the bowel contents. It is not known if terfenadine is dialyzable.

Treatment of the signs and symptoms of overdosage should be symptomatic and supportive after the acute stage. Oral LD₅₀ values for terfenadine were greater than 5000 mg/kg in mature mice and rats. The oral LD₅₀ was 438 mg/kg in newborn rats. Single doses as high as ten times (600 mg) the recommended therapeutic dose in adults have been well tolerated.

DOSAGE AND ADMINISTRATION: The usual dosage for adults and children 12 years and older is 60 mg (1 tablet) twice daily.

PRESENTATION: TELDANE tablets are available in blister strips in packs of 20. Each TELDANE tablet is white, round, flat faced and bevel edged with "M" on one side and a break line and 084 on the other. Each tablet contains 60 mg terfenadine.

ADVERSE EVENTS REPORTED IN CLINICAL TRIALS

ADVERSE EVENT	PERCENT OF PATIENTS REPORTING			
	CONTROLLED STUDIES* TELDANE N=781	PLACEBO N=665	ALL CLINICAL STUDIES** TELDANE N=1462	PLACEBO N=1478
Central Nervous System				
Drowsiness	9.0	8.1	8.5	8.2
Headache	6.3	7.4	15.8	11.2
Fatigue	2.9	0.9	4.5	3.0
Dizziness	1.4	1.1	1.5	1.2
Nervousness	0.9	0.2	1.7	1.0
Weakness	0.9	0.6	0.6	0.5
Appetite Increase	0.6	0.0	0.5	0.0
Gastrointestinal System				
Gastrointestinal Distress (Abdominal distress, Nausea, Vomiting, Change in Bowel Habits)	4.6	3.0	7.6	5.4
Eye, Ear, Nose and Throat				
Dry Mouth/Nose/Throat	2.3	1.8	4.8	3.1
Cough	0.9	0.2	2.5	1.7
Sore Throat	0.5	0.3	3.2	1.6
Epistaxis	0.0	0.8	0.7	0.4
Skin				
Eruption or itching	1.0	1.7	1.6	2.0

* Duration of treatment in "CONTROLLED STUDIES" was usually 7-14 days at a dose of 60mg twice daily.

** Duration of treatment in "ALL CLINICAL STUDIES" was up to 6 months.



Sedation-free relief of allergic rhinitis

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Product information as of February, 1986.

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APOTEX_AZFL 0061714

ISOPTIN®

The antihypertensive. Because you want antihypertensive effect, not side-effects.

PRESCRIBING INFORMATION VERAPAMIL HYDROCHLORIDE

Indications:

- Hypertension
- Angina of effort
- Angina at rest
- Vasospastic angina (including Prinzmetal's variant angina)
- Tachyarrhythmias including paroxysmal supra-ventricular tachycardia
- Atrial fibrillation } with rapid ventricular response
- Atrial flutter }

Use in Pregnancy:

Only limited information is available on the use of ISOPTIN in pregnancy. The drug should therefore not be used in pregnant women, or those likely to become pregnant, unless the expected benefits outweigh any potential risks.

Use in Lactation:

The use of ISOPTIN during lactation should be avoided unless expected benefits outweigh any potential risk. However, preliminary results indicate that verapamil may reach concentrations of 10-65 ng/ml in the milk of nursing mothers. Such concentrations are unlikely to produce clinical effects in the infant.

CONTRAINDICATIONS:

Cardiogenic shock.
Recent myocardial infarction.
Known hypersensitivity to verapamil hydrochloride, or to aspirin or azo dyes, since the oral formulations contain tartrazine.

WARNING:

Use verapamil hydrochloride with caution in conjunction with beta adrenergic blocking drugs as the myocardial depressant effects of each drug may be additive.

PRECAUTIONS:

In sick-sinus syndrome and second and third degree heart block, ISOPTIN may further impair SA or AV nodal function respectively.

In the presence of cardiac failure full compensation with cardiac glycosides should be ensured prior to administration of ISOPTIN.

Caution is necessary in initiating treatment, or increasing dosage of ISOPTIN in patients with cerebrovascular accidents, sinus bradycardia, heart block and hypotension.

INTERACTIONS:

Both ISOPTIN and beta blocking drugs may slow AV conduction and depress myocardial contractility by different mechanisms. Cardiac function, heart rate and rhythm, and blood pressure should be closely monitored during simultaneous oral administration.

Other anti-arrhythmic, anti-hypertensive and cardiodepressant drug therapy should be reviewed prior to introduction of ISOPTIN.

ISOPTIN has been reported to increase plasma levels of digoxin.

Physicians should be alert for symptoms of possible digitalis intoxication, and may wish to measure digoxin levels in plasma. However, extensive experience indicates that this possible interaction is of only slight clinical relevance.

DOSAGE AND ADMINISTRATION:

In mild and moderate hypertension the usual starting dose is one 80 mg tablet two or three times a day. The maintenance dose may be adjusted to two 80 mg tablets two or three times a day.

Usual maintenance dose 160 mg twice daily.

The individual dose and frequency of dosing, should be determined in accordance with the indication and individual patient response.

Paediatric: Dose range 40-360 mg per day in 2 or 3 divided daily doses according to age and response.

Geriatric: } The recommended daily dosage

Renal failure: } is usually well tolerated.

Hepatic failure: } Caution should be exercised when initiating therapy since the pharmacological action of ISOPTIN may be increased or prolonged by hepatic insufficiency.

ADVERSE REACTIONS:

ISOPTIN is usually well tolerated.

More common reactions include constipation, flush, headache and dizziness.

Hypotension, bradycardia, development or worsening of symptoms of cardiac failure and rhythm disturbances have been reported.

Rarely, non-specific immunological reactions such as skin rashes may occur.

Individual hypersensitivity to verapamil in the absence of accumulation or overdosage, has been described.

OVERDOSAGE:

Symptoms: Bradycardia, cardiac arrest, second and third degree AV block, hypotension and myocardial insufficiency.

Treatment: Serious oral overdosage should be treated by induced emesis, or gastric lavage and aspiration, prior to admission to intensive care.

Repeated intravenous calcium gluconate (10 ml, 10% solution), and sodium bicarbonate if metabolic acidosis develops represent logical therapy.

Intravenous fluids and cardiorespiratory support may be necessary. Dialysis would not seem potentially useful.

Other treatment, selected in accordance with the presenting symptoms, may include atropine, isoprenaline (isoprotenerol), dopamine, cardiac glycosides and noradrenaline (norepinephrine).

Recorded overdoses survived include a 14 year old girl who ingested 24 g and a 28 year old woman who took 36 g.

PRESENTATION:

ISOPTIN 40 mg (100 tablets) NHS General Benefit - 100 tablets, 5 repeats.

ISOPTIN 80 mg (100 tablets) NHS General Benefit - 100 tablets, 5 repeats.

ISOPTIN 160 mg (60 tablets) NHS General Benefit - 60 tablets, 5 repeats.

Full Prescribing Information available on request.



Distributors: Knoll Pharma Division, Schering Pty Limited
Knoll (Inc in NSW) 9-10 Wood Street Tempe NSW 2044 Australia

isoptin® is a registered trade mark of Knoll AG, the pioneers of calcium antagonism.

... Fixed Drug Combinations

atropine in each tablet. The rationale is that the unpleasant anticholinergic side effects of atropine would discourage anyone from taking an excess of tablets on more than one occasion. Whether this is a successful ploy is not really known since habituation has not been reported with usual therapeutic doses [7]. Furthermore, it does have some disadvantages as overdosage in young children has resulted in atropine poisoning as well as severe respiratory depression [8].

Cost

The factors determining the costs of therapeutic drugs are complex and vary from country to country and from time to time. It is virtually impossible to do all the sums taking into account the costs of prescription and dispensing fees and government rebates. Overall it is probable that combination products are cheaper than the individual components prescribed separately but there is evidence both for [6] and against this view [9].

Potential Disadvantages of Fixed Drug Combinations

There is an almost equal number of theoretical disadvantages to fixed combination drugs as shown in table II.

Fixed Dose Ratio

One of the major problems is that the prescribing doctor loses flexibility in patient management. For

Table II.

Potential disadvantages of fixed drug combinations

Fixed dosage ratio (inflexibility)

Incompatible pharmacokinetics

Increased toxicity

Inappropriate combinations

Physician ignorance of content

Brand names

... Fixed Drug Combinations

many drugs such as insulin or β -blockers the effective dose varies between patients and in different disease states, e.g. in hepatic or renal failure, doses of many drugs must be carefully adjusted. It is not sufficient to defend fixed drug combinations by saying that many doctors do not adjust doses anyway and do not have the knowledge of pharmacokinetics to do so accurately. Bad prescribing cannot be justified by ignorance, rather it is an argument for improving doctors' knowledge of clinical pharmacology.

Incompatible Pharmacokinetics

Some combination drugs such as co-trimoxazole have their components deliberately selected to have similar half-lives and clearance rates. This is not the case with many other combinations, particularly the older ones, and this can produce very different patterns of drug accumulation [1]. If the 2 component drugs are prescribed separately there is scope for different dosage intervals. However, sometimes pharmacokinetic differences are irrelevant as in the case of β -blockers and diuretics where biological effect is quite different from half-life. Sometimes it could even be advantageous to have 2 drugs such as analgesics with differing onsets and durations of actions.

Increased Toxicity

The use of 2 drugs will always increase the risk of adverse drug reactions both idiosyncratic and pharmacological. The problem with combination drugs is trying to decide which of the 2 (or more) components has caused the problem. If both have to be stopped the patient may be denied a useful and safe drug in the future. In some circumstances patients may be exposed to additional ingredients with little therapeutic benefit and major potential side effects. For example, many over-the-counter preparations for coughs and colds contain indirect acting amines, e.g. phenylpropanolamine, which can induce marked hypertension [10].

Inappropriate Combinations

Any drug combination introduced to Australasia in the past 10 years is likely to be therapeutically appropriate but this is not true of many of the older

preparations and it is clearly vital for a prescribing doctor to know what components are contained in a given formulation.

Physician Ignorance

An alarming Canadian study asked a selected group of doctors to state the names of the ingredients of several drug combinations which they regularly prescribed [11]. The best results were a 66% correct response for a combination of an antianginal drug with chlorthalidopoxide (incidentally a combination that would be considered highly undesirable in Australasia). Only 33% of the subjects knew the content of various compound analgesic tablets. The message is obvious: do not prescribe a drug unless you are certain of its individual components. This will avoid problems such as prescribing aspirin to a patient on anticoagulants.

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Brand Names and Generic Names

Patents for drugs have short lives but brand names go on forever and it is a possible marketing strategy to produce a combination product with a clearly identifiable brand name. It is then very difficult for another company to market a generic equivalent for the item although in the case of some compound analgesics generic competitors do exist. As a marketing

... Fixed Drug Combinations

exercise, combination products are often very successful and this fact should not be confused with efficacy. From a practical point of view there is already considerable confusion between generic and brand names for single substances and the confusion is even greater with combination drugs. Thus, without care, prescribing one combination instead of another could be introducing a new substance. There is currently a move in the UK to give compound preparations, such as analgesics, generic names but this seems to be causing even greater confusion [12]. The use of single substances at least reduces this problem.

Thus general considerations produce very few good reasons for using combination products.

Specific Considerations

It is not possible to review the pros and cons of fixed drug combinations for all indications and I will limit discussion to commonly prescribed oral formulations and others likely to be marketed in the near future. Table III lists those oral combinations that are pharmacologically appropriate. Topical preparations such as skin creams and eye drops will not be considered.

Antibiotics

Co-trimoxazole has been discussed above and still has a useful role in spite of recent doubts about whether true synergy occurs and opinions that trimethoprim alone is as effective [5].

Tetracycline-nystatin combinations have become very popular in the treatment of minor infections. In Australia in 1980 there were more than 1.6 million prescriptions written on the pharmaceutical benefits scheme for such a combination and that is, of course, an underestimate of total prescriptions. Nystatin is not absorbed and it is included to act as a local antifungal agent to prevent superinfection provoked by the tetracycline. The concept is an interesting one but unfortunately there is no clear relationship between *Candida* in the faeces and gastrointestinal symptoms in patients receiving tetracyclines. The combination does not result in reduced side effects as compared with tetracycline alone [1] and there seems little point in

Table III.

Pharmacologically appropriate combination oral agents

Antacids containing magnesium and aluminium

Levodopa with benserazide

Levodopa with carbidopa

Oral contraceptive preparations

Sulphadoxine and dapsone

Sulphadoxine and pyrimethamine

Trimethoprim and sulphamethoxazole

Amoxycillin and clavulanic acid

Imipenem and cilistatin

using an expensive product where a cheaper one would suffice.

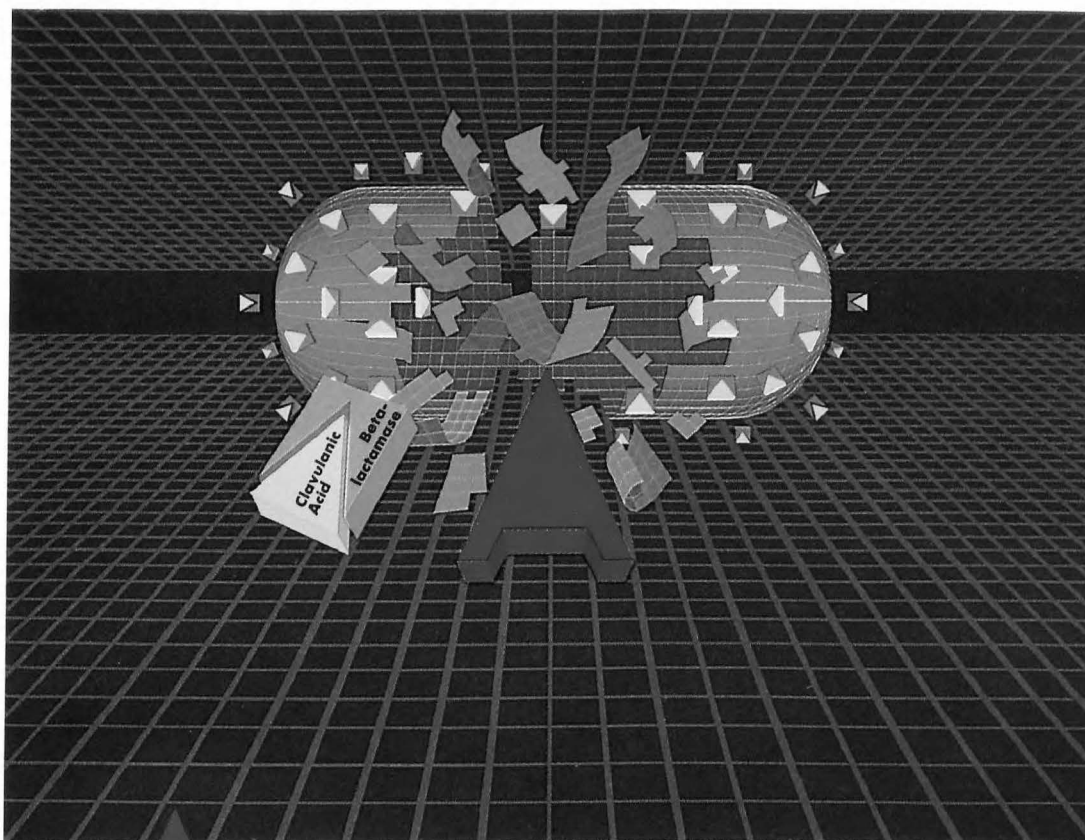
The combination of amoxycillin with clavulanic acid, the β -lactamase inhibitor, is an attractive one. The situations in which it is the antibiotic of choice have not yet been fully defined but it appears to be an effective oral therapy for gonorrhoea thereby avoiding the need for parenteral therapy. It is also being used successfully for persistent urinary tract infections. The role of other penicillins, such as ticarcillin, combined with clavulanic acid is much less certain. Sulbactam, another β -lactamase inhibitor, is being used in combination with a variety of penicillins and with cefoperazone but the drugs seem to have little advantage over existing antibiotics.

Imipenem/cilistatin has a broad spectrum of antimicrobial activity but is not yet available in Australasia. Pharmacologically the combination is a logical and neat one but its appropriate therapeutic role has not yet been defined. It looks likely to be a costly competitor for the already expensive third generation cephalosporins.

Compound Analgesics

These are widely used both as prescription drugs and as over-the-counter items. There is very little evidence that any analgesic combination is better than

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¹Wren BG: Oestrogen replacement therapy. *Med J Aust* 142 (suppl):S1-S15, 1985.

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its individual components taken separately and the majority of clinical trials have failed to show any increased efficacy [13]. Furthermore analgesics are a common choice of drug for ingestion by self-poisoners and combined preparations such as those containing dextropropoxyphene and paracetamol increase the chances of death by causing 2 different types of toxicity [14]. There may be a few patients who do better on combination analgesics in spite of the population-derived, statistical evidence of controlled trials. However, it is good sense to try single drugs initially and, only if they fail, move on to more complex preparations, i.e. combination analgesics should always be second line therapy.

Diuretic Combinations

Combinations of potassium-sparing and potassium-losing diuretics are very popular. They are used to treat both hypertension and heart failure. A review in 1980 concluded that most patients taking a diuretic for either indication do not develop clinically significant hypokalaemia and therefore do not require potassium replacement [15]. Since then there have been suggestions that even mild hypokalaemia could increase the risk of sudden death from ventricular arrhythmias and that thiazide-induced hypokalaemia might increase mortality sufficiently to outweigh any benefits of treating mild hypertension [16].

The issue is a complex one but has recently been very well reviewed [17]. The conclusions reached were: 'Most patients with hypertension or heart failure on treatment with a low dose of thiazide or loop diuretic do not need a potassium-sparing diuretic and no epidemiological evidence exists to support their routine use. Their use may be justified in patients at particular risk of the cardiac effects of hypokalaemia and hypomagnesaemia ... combination preparations appear convenient for the patient but make treatment difficult to titrate'. In other words potassium replacement is needed far less often than it is prescribed and when it is needed potassium sparing diuretics may be preferable to potassium supplements. However, they can be used as a separate tablet and combination therapy is rarely the treatment of choice since the relative ratios of the 2 types of diuretic will vary from patient to patient.

Hypertension

Most patients with hypertension are treated with more than one drug. It is a situation where long term therapy is needed for an asymptomatic condition and compliance is therefore a major problem. At least one authority has suggested that fixed combination therapy might be an appropriate solution [18] but there is little evidence that it would be an advantage.

The study by Asplund et al. [4] not only showed no improvement in compliance but found that patients on combination or separate therapy for 4 months showed no difference in control of blood pressure or in incidence of side effects. Since fixed combination compounds remove all flexibility in dose variation of a diuretic (which is usually the same dose for all patients) and a β -blocker (which is commonly different for different patients), it is difficult to be enthusiastic about such formulations. However, numerous β -blocker/diuretic combinations are already available in the UK and 2 are on the market in Australia. Neither is on pharmaceutical benefits which reflects the view of the regulatory authorities. I anticipate that these products will be promoted energetically and doctors will need to have very clear views on the relative advantages and disadvantages of such combinations. As indicated above, potassium-losing and potassium-sparing diuretic combinations are rarely the treatment of choice for hypertension.

Iron Folate Combinations

Routine prophylaxis of iron and folate deficiency anaemias of pregnancy is widely practiced but the need for it on a routine basis in developed countries has been questioned [19]. In normal women the haemoglobin level will rise if iron is taken but there is no evidence that the woman feels better or that the foetus fares better [20]. Megaloblastic anaemia due to folate deficiency is even rarer. Thus there seems little justification for the administration of folate since there is no good evidence that routine folate supplements will raise the haemoglobin level in patients without anaemia [21] and there is no evidence for reduction in the incidence of pregnancy complications [20].

Use of combined iron and folate preparations should therefore be confined to anaemic women who

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are thought to be poor compliers or those who because of social circumstances are at dietary risk of anaemia in pregnancy. It should also be borne in mind that many of the marketed preparations are more expensive than their individual components.

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Bronchodilator Aerosol Combinations

Asthmatic and bronchitic patients often carry 3 or 4 inhalers containing sympathomimetic drugs, anticholinergic agents, corticosteroids or sodium cromoglycate. This can be inconvenient and often leads to confusion about which inhaler to use in a given situation. Pharmaceutical companies are therefore producing a variety of combination products containing β_2 -agonist drugs plus anticholinergic agents or corticosteroids.

Patients and doctors may find it attractive to reduce the number of inhalers prescribed but it is difficult to justify the practice on pharmacological or therapeutic grounds. Virtually all asthmatic patients, and the majority of bronchitics, will achieve maximal bronchodilation with a β_2 sympathomimetic agonist agent. The role of the anticholinergic drug, ipratropium bromide, has not been defined and there is no good evidence of a synergistic effect between the 2 types of bronchodilators [22]. Ideally the combination should only be used if a synergistic effect has been demonstrated for an individual patient [23].

Combinations of β_2 agonist drugs and corticoste-

roids are even less desirable because the 2 agents have completely different functions in the management of asthma. Prescribing them in combination would remove any chance of educating patients on the difference between prophylaxis and symptomatic relief. In addition there are times when patients are well controlled by regular inhalation of corticosteroid alone and need only infrequent doses of β_2 agonist. They would be getting an unnecessary dose of the bronchodilator drug. Conversely patients using additional doses of the aerosol to relieve acute bronchospasm would get an unnecessarily high dose of corticosteroid with the possibility of side effects. They would therefore need to carry an extra inhaler for acute use and this would negate the point of the combination [24]. Such combinations, therefore, have superficial appeal but cannot be recommended for general use.

Conclusions

Any conclusion has to be made on the basis of rather limited evidence but the questions that should be asked before prescribing any combination product are:

- Does the patient need both drugs or would one be adequate?
- What drugs and how much of each does the formulation contain?
- May it become necessary to change the dose of one of the component drugs without the other?
- Do the pharmacokinetic properties of the components fit well together?
- Are the components likely to have additive side effects?
- Do the components have any known adverse interactions?
- Does tolerance develop to any of the component drugs?
- Is compliance likely to be an important problem, as in hypertension, or is treatment symptomatic as in pain?
- Does the cost of the combination exceed that of the components prescribed separately in the same doses?

In spite of the many reservations described above there is no doubt that pharmaceutical companies will

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be producing more combination preparations and marketing them energetically. It is likely that the regulatory authorities in Australasia will only allow a few combination products onto the market and even fewer onto the pharmaceutical benefits list. For those which do become available, prescribing doctors will need to be aware of all of the issues involved and to make decisions about each product on an individual patient basis.

A combination should only be prescribed if each component is known to be necessary for the desired effect. In addition the advantages of using a combination, rather than a single drug should outweigh the added risks of using 2 or more drugs.

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