drug accumulation after multiple dosing. This is in accordance with the findings of Hull & Sarubbi (1976) who had appreciated the unreliability of their therapeutic guidelines in the presence of severe renal failure ($CL_{cr} < 10$ ml/min) and therefore stressed the necessity of serum concentration measurements in this situation. As an example, let us consider a patient with CL_{cr} of 5 ml/min who is receiving a dosage regimen recommended by the above authors (loading dose 100 mg, maintenance dose 50 mg gentamicin every 24 h). Using the pharmacokinetic parameters reported for gentamicin by Schentag *et al.* (1977) the predicted serum concentrations 3 and 24 h after the second dose are 5.0 and 2.4 mg/l, respectively. After 10 days of therapy the 3 and 24 h serum concentrations can be calculated as 7.8 and 5.3 mg/l, respectively. The disproportional rise of the trough level (220%), compared

with the increase in the peak serum concentration (156%), illustrates the prolongation of the apparent half life and is indicative of drug accumulation in the body.

Until more data are available allowing a design of dosing aids that account for the multicompartment kinetics of gentamicin and tobramycin close monitoring of serum concentration throughout the course of therapy is advisable in patients with severe renal failure in order to assure efficacy and to avoid toxicity.

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INTERACTION BETWEEN LEVAMISOLE AND ASPIRIN IN MAN

Levamisole, an antihelminthic and stimulant of cell mediated immunity, has recently been shown to be useful in the treatment of rheumatoid arthritis (Huskisson, Dieppe, Scott, Trapnell, Balme & Willoughby, 1977; Runge, Pinals, Lourie & Tomar, 1977).

Since levamisole is likely to be used in rheumatoid

arthritis with the concurrent administration of other antirheumatic drugs, especially the nonsteroidal anti-inflammatory agents, the possibility of pharmacokinetic drug interaction exists. Laidlaw (1976) has reported a rise in plasma salicylate levels in a patient with rheumatoid arthritis when levamisole was administered concurrently with aspirin. The aim of

the present study was to examine the nature and significance of this reported interaction between levamisole and aspirin.

Nine healthy adults were given sustained release aspirin (SRA, 650 mg Boots) 3.9 g/day in two divided doses for 3 weeks. Levamisole 50 mg three times a day was added to this regime for 7 days starting on either day 8 or 15. (Five subjects received levamisole starting day 8 and four subjects starting day 15). Two subjects withdrew without completing the study.

Blood was collected 6 h after aspirin ingestion on day 7 of each treatment week. Saliva was collected at 4 and 6 h after aspirin administration on days 6 and 7 of each treatment week. Plasma salicylate levels were determined by the method of Rowland & Reigelman (1967). Each plasma level reported in this work is the mean of four determinations. Salivary salicylate levels were determined by the method of Graham & Rowland (1972).

Since salicylate levels vary greatly between individuals (Graham, Champion, Day & Paull, 1977), the effect of levamisole on salicylate levels was assessed using each subject as his own control. The difference between the plasma salicylate levels of the

day immediately prior to the commencement of levamisole treatment and on day 7 of the levamisole treatment week was determined for each subject (Table 1). The significance of the difference between salicylate levels with and without concurrent levamisole therapy was assessed using a paired Students *t*-test. A similar analysis was used in examination of the salivary data (Table 2). The salivary salicylate levels shown in the table are those obtained 6 h after aspirin ingestion and similar levels were noted at 4 h.

In this study, aspirin was administered for at least 1 week prior to levamisole therapy to ensure that analysis of changes in salicylate levels during levamisole therapy was made in comparison to steady-state plasma salicylate levels. Salivary salicylate levels were found to vary from day to day but similar changes were noted both before and during levamisole treatment.

An analysis of this difference for plasma and saliva (Tables 1 and 2) by the paired *t*-test showed no significant change in salicylate levels of subjects prior to levamisole treatment compared to salicylate levels during levamisole treatment.

Table 1 The difference between plasma salicylate levels immediately prior to starting levamisole treatment and on day 7 of the levamisole treatment week.

Subject	Age (years)	Sex	Plasma salicylate levels ($\mu\text{g/ml}$)		Differences in salicylate
			Day prior to levamisole treatment	Day 7 of levamisole treatment	
JW	24	F	245	265	+ 20
EW	22	F	250	138	- 112
LA	21	F	167	222	+ 55
DM	23	M	43	67	+ 24
RW	21	M	153	156	+ 3
HM	22	F	254	221	- 33
ML	24	F	124	108	- 16
Mean			176	168	- 8

Table 2 The difference between salivary salicylate levels immediately prior to starting levamisole and on days 6 and 7 of levamisole treatment week

Subject	Salivary salicylate levels (mg/ml)					
	Day 6 of week			Day 7 of week		
	Prior to levamisole	Of levamisole treatment	Difference	Prior to levamisole	Of levamisole treatment	Difference
JW	18.8	13.8	-5.0	8.4	10.4	2.0
EW	9.5	15.9	6.4	16.7	11.3	-5.4
LA	8.5	8.3	-0.2	9.9	6.8	-3.1
DM	—	—	—	0.5	2.1	1.6
RW	8.3	12.0	3.7	—	—	—
HM	—	—	—	13.6	12.6	-1.0
ML	5.7	3.2	-2.5	4.4	7.2	2.8
Mean	10.2	10.6	0.5	8.9	8.4	-0.5

Figure 1 The salivary salicylate/plasma salicylate ratio before (△) and during (▲) levamisole treatment.

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COMPARATIVE DOSES OF FOUR ANTIHYPERTENSIVE DRUGS

For various reasons, both clinical and theoretical, it is often valuable to know the equipotent doses of various antihypertensive drugs. The continuing interest in this topic has again been demonstrated by the recent paper from Wilcox (1978) and the subsequent correspondence. As part of another study (Griffith, James, Newbury & Woollard, 1979) we have been looking at the effects of four commonly-used drugs (labetalol, metoprolol, oxprenolol and sotalol) administered sequentially to hypertensive patients, and although the design was not specifically tailored to compare potency, it is nevertheless possible to draw some conclusions about the relative antihypertensive effects of the four drugs.

Patients newly-discovered to have essential hypertension were considered for inclusion. Blood pressure was measured with a standard mercury sphygmomanometer, taking the fourth Korotkoff sound as the diastolic pressure. Measurements were taken after the patient had rested in the supine position for 5 min, and again after 2 min standing. Hypertension was defined as a diastolic pressure greater than 100 mm Hg calculated from the mean of the two readings on three separate occasions, i.e. the mean of six values. Patients were excluded if they had contraindications to β -adrenoceptor blocking drugs; if they had concomitant systemic disease; or if they were on any other medication.