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Long-Term Management of Rheumatoid Arthritis with Disalcid®

Prim dr Franc Fazarinc, *Chief, Department of Medicine, General Hospital, Calje, 63000 Yugoslavia*

Stephen N Steen, ScD, MD, *Professor of Anesthesiology, UCLA School of Medicine, Harbor General Hospital Campus, Torrance, California 90509, U.S.A.*

Disalcid®, a salicylic acid pro-drug, was administered for 3 months to eighteen rheumatoid arthritis patients, with monitoring of clinical response, side-effects and laboratory changes. The drug produced a satisfactory to excellent response in fourteen patients and was unsatisfactory in four.

Gastric side-effects occurred in three patients and allergic reaction in one. Serum salicylic acid concentrations were adequately maintained between 15 to 25 mg/100 ml.

Funduscopic monitoring revealed one retinal defect in a patient with hypertension. Laboratory examinations, blood chemistry and urine analyses remained within normal limits during the 12-week trial.

Introduction

Renewed attention is being focused on salicylsalicylic acid*, a disalicylic acid molecule producing on a weight-for-weight basis nearly 30% more salicylic acid than simple aspirin. The reasons for this interest are manifold: the drug causes no gastric blood loss (Leonards 1969, Cohen 1979) and little gastric irritation, it does not share the thrombopathic proclivities of aspirin, nor does it alter plasma proteins by a trans-acetylation known to occur when regular aspirin is used (Singleton 1980). These important safety features suggest the drug be considered for the long-term management of such chronic inflammatory diseases as rheumatoid arthritis.

Available clinical data, however, are mostly from short-term investigations (Nordqvist 1964, Deodher, McLeod & Dick 1977, Ré 1979); the longest study was for 6 weeks but failed to include laboratory monitoring (Regalado 1978). Thus, although the drug has been shown to have efficacy comparable to that of aspirin, little information exists with regard to long-term effects on haematological and organ systems. The present study was designed to provide such information from a small group of rheumatoid arthritis patients.

*Disalcid® – Riker Laboratories, Inc, 19901 Nordhoff St, Northridge, CA 91324, U.S.A.

Address for Reprints:
Prim dr Franc Fazarinc
Chief, Department of Medicine,
General Hospital,
Calje, 63000 Yugoslavia

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Table 1

Patient demographic data

Sex		Age (yr)		Weight (kg)		Disease duration (yr)	
M	*F*	*Mean*	*Range*	*Mean*	*Range*	*Mean*	*Range*
3	15	45·5	26–63	75	58–112	6·6	< 1–20

Materials and Methods

Patients entering the study had an established diagnosis of rheumatoid arthritis (RA). Their mean age was 45·5 years and ranged from 26 to 63 years (Table 1); average weight was 75 kg, ranging from 58 to 112 kg. Duration of RA ranged from less than 1 year to 20 years, with a mean of 6·6 years. Each patient had normal cardiovascular, pulmonary, hepatic and renal function as established by laboratory and physical examinations. None were undergoing anticoagulant therapy at the time of the study. Funduscopic examinations were also made before and after treatment.

Clinical response was determined by the usual evaluations of grip strength, pain intensity, walking time, etc, and classified as excellent, satisfactory or unsatisfactory. Random tests were done to determine the adequacy of serum salicylic acid concentrations. Laboratory monitoring further consisted of full haematological and blood chemistry tests along with urinalyses. All evaluations were made before and at 2, 4, 8 and 12 weeks after taking salicylsalicylic acid. The drug dose was two tablets three times a day (3 g), with allowances for titration between 2 and 4 g daily.

Results

Adequate clinical response was observed between 2 and 12 weeks in fourteen patients. In nine patients the response was excellent and in five it was satisfactory. Four patients were rated unsatisfactory: one was found to have gout and treatment was changed; another had an undisclosed history of aspirin allergy; the third had gastritis and the fourth was despondent and simply gave up her treatment.

Funduscopic examinations during the 40.5 patient-months of salicylsalicylic acid use in this study were negative except for one individual. Follow-up eye examination in this 80-year-old woman revealed incipient retinal degeneration attributable to coexisting hypertension; her clinical response to the drug was satisfactory. Overall, most of the patients had a favourable clinical change in approximately 7 weeks, some as early as 2 weeks. One elderly female patient with a 3-year history of RA had a clinically excellent response despite complicating severe gastritis. Although she wanted to continue treatment and, if possible, control the side-effects, she was changed to another medication after 4 weeks.

Underlying the good clinical response seen in 78% of these patients was the adequate maintenance of serum salicylic acid concentrations (Table 2). No attempt was made to closely monitor these concentrations; similarly, blood samples were drawn at random times in relation to the last dose of drug. Despite this, clinical and laboratory evidence indicate general attainment of therapeutically effective serum levels of drug as measured by total salicylates.

Patients maintained at such levels using aspirin and perhaps other salicylic acid precursors often exhibit serum enzyme

Table 2

Serum salicylic acid (SA) concentrations

Treatment week	Mean SA concentrations (mg%)	Number of patients
2	20·3	9
4	23·0	3
8	14·7	7
12	17·0	6

	Disease duration (yr)	
	Mean	Range
	6·6	< 1–20

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A) concentrations

SA ntrations (mg%)	Number of patients
	9
	3
	7
	6

Table 3

Mean serum transaminase and lactic dehydrogenase levels* (units/ml) during 3 months of salsalate administration

	Transaminases		
Treatment week	SGOT (N)	SGPT (N)	LDH (N)
Pre-drug	6·8 (16)	5·3 (15)	174·8 (14)
2	7·4 (15)	3·9 (14)	209·9 (14)
4	9·0 (14)	10·8 (14)	219·0 (14)
8	9·8 (11)	10·2 (11)	212·2 (11)
12	13·1 (11)	12·4 (11)	183·2 (11)

*See Table 4

Table 4

Normal values and methods for SGOT, SGPT, and LDH

Test	Method	Values
SGOT	Optimised kynetic	18 mU* (female) 21 mU (male)
SGPT	Optimised kynetic	21 mU (female) 33 mU (male)
LDH	Boehringer	120–260 mU

*Milli-unit

increments. We noted pre-drug mean SGOT and SGPT concentrations of 6·8 and 5·3 units/ml, increasing after 12 weeks to 13·1 and 12·4 units/ml; lactic dehydrogenase likewise showed a modest increment, mean concentrations peaking at 4 weeks and returning to almost pre-drug levels at 12 weeks; all still well within their respective normal limits (Table 3).

Discussion

Salsalate is a good alternative to regular aspirin treatment of RA patients, especially those with histories of gastric intolerance or bleeding, haemostatic disorders, or so-called 'transaminitis' or salicylate hepatitis. Its clinical efficacy is comparable to any other salicylic acid precursor and the drug seems to provide many safety advantages. Chiefly, these are less gastric irritation (Leonards 1969, Cohen 1979, Thune 1968, Liyanage & Tambar 1978, Edmar 1971), lack of effect on platelet aggregation or bleeding time (Singleton 1980, Thune 1968, Rothschild 1979, Nordqvist 1976, Pinkard, Hawkins & Farr 1968) and reduced allergenicity (Singleton 1980, Pinkard *et al* 1968, Farr 1970).

This 3-month trial demonstrated no prominent effect on serum enzymes and other laboratory parameters. Although small increments of SGOT and SGPT occurred, they were not abnormal. Nor did they meet other criteria constituting adequate reason for withdrawal from a study established recently at the Hepatotoxicity Fogarty International Conference (1977). In fact, a number of clinicians have commented on decrements of SGOT and SGPT during continued salsalate therapy.

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