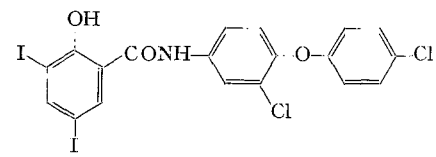
A New Agent for the Treatment of Liver Fluke Infection (Fascioliasis)

The importance of anthelmintic effectiveness against the immature stages of *Fasciola hepatica L.* has been stressed[1,2]. Several agents with established utility for control of mature fluke infections are also effective against immature flukes, but only at doses near the toxic level. Some newer agents represent progress toward a greater safety factor in the therapy of acute fascioliasis, with safety indices, as defined by BORAY[3], as high as 1.5 against 4-week-old infections and 3.0 against 6-week-old flukes in sheep.

LIENERT[4–6] reported the effectiveness of dichlorosalicylic acid and of a combination of 5,4'-dibromosalicylanilide and 3,5,4'-tribromosalicyl anilide against mature liver fluke infections in cattle. More recently, another salicylanilide, oxyclozanide (3,5,6,3',5'-pentachloro-2'-hydroxy-salicylanilide) was introduced for use against mature fluke infections in sheep at a dosage of 15 mg/kg[7]; and clioxanide (2-acetoxy-4'-chloro-3,5-diiodobenzanilide) was reported[8] active against mature flukes at 15 mg/kg and against 6-week-old flukes at 48 mg/kg.

Following investigation of the salicylic acid lead, we have discovered that a series of phenoxysalicylanilides possess high potency against both mature and immature fluke infections in sheep. More than 200 examples have been prepared for evaluation; and one, 3,5-diiodo-3'-chloro-4'-(*p*-chlorophenoxy)-salicylanilide (I), shows exceptional potency and substantially improved safety for the treatment of immature infections. 3,5-Diiodo-3'-chloro-4'-(*p*-chlorophenoxy)-salicylanilide (I) was obtained by reaction of 3,5-diiodosalicylic acid with 3-chloro-4-(*p*-chlorophenoxy)-aniline in refluxing chlorobenzene (3 h), with phosphorus trichloride as the condensing agent. It is a colorless crystalline solid, mp 168–170°, moderately soluble in acetone and acetonitrile and insoluble in water.



(I)

The anthelmintic activity of I was first demonstrated in albino rats harboring mature *Fasciola hepatica*. In subsequent tests in sheep, the drug was found to be highly active against mature flukes when given orally at dosages of 5–7.5 mg/kg. It was also effective against mature flukes in cattle when dissolved in dimethylformamide or polyethylene glycol, and injected parenterally at a dosage of 3 mg/kg or intraruminally at 6 mg/kg.

As in the case of other fasciolicidal drugs, treatment of immature infections with I requires higher dosages than treatment of mature infections. In sheep with experimental infections of 6 weeks' duration, I was highly effective (> 90% eradication of flukes) at a dosage of 12.5 mg/kg. Against 4-week-old fluke in sheep, it was moderately effective (> 50% efficacy) at 25 mg/kg and fully effective (> 90% efficacy) at 50 mg/kg.

Sheep suffering from liver fluke infection are less tolerant to drugs than are non-infected sheep, and the practical therapeutic index of a drug thus depends upon the severity of the infection. No deaths occurred among 10 non-infected sheep given compound I at a dosage of 200 mg/kg. In sheep with natural liver fluke infections, death occurred in some animals given a dosage of 200 mg/kg, but in none of those given 100 or 150 mg/kg. In sheep with severe infections (inoculated with 1000 metacercariae each, 8 weeks prior to treatment) one sheep died out of 15 treated with I at a dosage of 100 mg/kg.

Some of the non-infected animals that survived treatment with I at a dosage of 200 mg/kg, and some of the infected sheep that received dosages of 100 mg/kg, or more, showed signs of ocular toxicity. Apart from minor scouring, no toxic signs were observed in non-infected animals treated with a dosage of 100 mg/kg, or in severely infected (1000 metacercariae) animals given dosages up to 60 mg/kg 8 weeks after inoculation. Naturally infected calves have tolerated dosages of 150 mg/kg, repeated 3 times at monthly intervals, with no signs of toxicity. The safety of this salicylanilide, like that of other drugs, can be expected to vary with the varying degree of parasitism encountered under field conditions, but the available data indicate that it is well tolerated even at the dosage required to achieve a high degree of efficacy against 6-week-old fluke.

In addition to its action against liver fluke, salicylanilide I has shown high activity, at dosages of 5–20 mg/kg, against natural and experimental infections of *Haemonchus contortus* in sheep (EGERTON et al., unpublished data). The compound was also active against *Hymenolepis nana* and *H. diminuta* in experimentally infected rodents, and has shown a modest degree of activity against *Schistosoma mansoni* in mice. It was inactive against the migrating larvae of *Ascaris suum* in experimentally infected mice.

Zusammenfassung. 3,5-Dijod-3'-chlor-4'-(*p*-chlorphenoxy)salicylanilid wird als ein neues Mittel gegen den Viehleberegel (*Fasciola hepatica*) beschrieben. In Schafen ergab eine Dosis von 5 mg/kg gegen geschlechtsreife Tiere und eine solche von 12,5 mg/kg gegen junge Leberegel eine hohe Wirksamkeit. Bei schwerem, akutem Leberegelbefall blieb sogar eine Dosis von 60 mg/kg ohne toxische Anzeichen. Ebenso wurde eine relativ hohe Wirksamkeit und eine gute Verträglichkeit bei der Behandlung von Leberegelinfektionen in Rindern festgestellt.

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