

A Retrospective Study on the Combination of Oral Ivermectin, Topical Anti-scabetic Agents and Keratolytic Agents in the Treatment in Crusted Scabies

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ABSTRACT

Background. This is a retrospective study on the efficacy of the combined treatment of oral ivermectin and topical treatment in crusted scabies.

Methods. Patients diagnosed with of crusted scabies in the Singapore General Hospital during the period December 2002 to October 2003 were included. Their data were retrieved from the case notes.

Results. There was a total of 8 patients. All had multiple co-morbidity and most were bed-bound. In 3 patients, crusted scabies cleared up after 1 dose of ivermectin. In two patients, scabies cleared up after 2 doses while in 2 patients, scabies cleared up after 3 doses.

Conclusion. Crusted scabies is a management problem due to the co-morbidity of the patient that impairs the patient's immunity and imparts difficulty in the application of topical treatment. The combination treatment of oral ivermectin and topical treatment offers a satisfactory solution to the treatment of crusted scabies.

Keywords: guidelines for treatment, ivermectin, scabies

INTRODUCTION

Scabies is a parasitic infestation caused by the mite *Sarcoptes scabiei* var *hominis*. The mite is an ectoparasite and is non-haematophagus. It measures about 1/3 mm in length and spends its entire life cycle in the human skin where it feeds and where the adult female lays its eggs. The mite can survive 2 to 3 days outside the host. In a common scabies infestation, there are 10 to 20 parasites per individual. Crusted scabies (formerly known as Norwegian scabies) is a massive scabetic infestation with inordinate number of mites due to inadequate host response. There is hyperplastic growth of the epithelium and this manifests clinically as generalised crusting or hyperkeratosis.

Scabies is highly contagious through direct person-to-person contact. The disease can also be acquired via sexual contact. It is an intensely pruritic condition mediated by a delayed type IV hypersensitivity reaction

to the mites, eggs and scybala (packets of faeces). The incubation period of the primary infestation is 15 to 20 days. In re-infestation, the incubation period is shorter. Infestation from infected personal items or clothing is more likely to be due to crusted scabies.

Scabies is a common problem worldwide and is a significant source of morbidity in nursing home residents. The standard approach to treatment involves the topical application of anti-scabetic agents. These include benzyl benzoate, malathion lotion and permethrin cream. When properly carried out, the cure rate approaches 100%. However, despite strict adherence to proper protocols of treatment, failure of clearance still occurs, especially in the treatment of crusted scabies.

Ivermectin is an antihelminthic agent used to treat onchocerciasis and strongyloidiasis. Millions of individuals in 30 countries have received ivermectin

Table 1. Home status, onset of symptoms to diagnosis and recent admission to hospital.

Name	Home/Nursing Home	Onset of Symptoms to Diagnosis (weeks)	Last Hospital Admission Prior to Diagnosis in Past 6 Months
OLY	Home	26	–
HTH	Home	8	–
TNC	Home	4	3 months ago
YCH	Home	52	7 months ago
CYF	Home	1	4 months ago
AB	Home	12	–
TAE	Home	2	–
AR	Nursing Home	4	1 month ago

Table 2. Clinical features and treatment.

Name	Extent of Skin Lesion	Significant Co-Morbidity	Duration of Positive Scrape (Days)	Dosage × Dose	Adjuvant Topical Treatment
OLY	Widespread, crusted papules, nodules on trunk and 4 limbs with predilection on breasts, umbilical and genital areas	Cushing syndrome Cirrhosis Diabetes mellitus Fracture neck of femur with infected prosthesis	22	15mg × 2	Malathion Benzyl Benzoate Salicylic Acid Ointment
HTH	Generalised exfoliative dermatitis	Renal transplant Diabetes mellitus Rheumatoid arthritis CMV Infection	39	12mg × 1 13.5mg × 1 27mg × 1	Malathion Benzyl Benzoate Salicylic Acid Ointment
TNC	Excoriated papules on trunk and 4 limbs Crusted lesions on hands and feet Burrows around wrists	Renal transplant Leiomyosarcoma EBV infection Recurrent UTI Neurogenic bladder	18	21mg × 3	Malathion Benzyl Benzoate Salicylic Acid Ointment
YCH	Crusted lesions in axillae and flexure of knees Papulosquamous eruption on trunk Vesicles on fingers	Multiple sclerosis Type II respiratory failure Neurogenic bladder Recurrent UTI	12	15mg × 1	Malathion Salicylic Acid Ointment
CYF	Crusted papules and nodules on lower limbs, neck, wrist, trunk Crusted lesions on nipples Vesicles in perineum	Acute lymphocytic leukemia with allogenic PBSC transplant CMV infection Disseminated aspergillosis Cerebral and pulmonary TB	8	21mg × 1	Malathion Benzyl Benzoate
AB	Erythematous papules and nodules on trunk and 4 limbs Hyperpigmented crusted papules over upper chest Burrows in wrists and finger webs	Hepatocellular carcinoma Diabetes mellitus	4	12mg × 1	Malathion
TAE	Crusted lesions on palms and finger webs Xerotic skin on trunk, upper limbs and flexure of knees	Dementia UTI Chest infection Acute renal failure secondary to dehydration	22	12mg × 2	Malathion Benzyl Benzoate Salicylic Acid Ointment
AR	Generalised erythematous scaly rash associated with crusted lesion on hands and feet	Diabetes mellitus Chronic renal failure Hypertension Dilated cardiomyopathy	14	18mg × 2	Permethrin Malathion Salicylic Acid Ointment



Fig. 1a. Crusts on the hand.

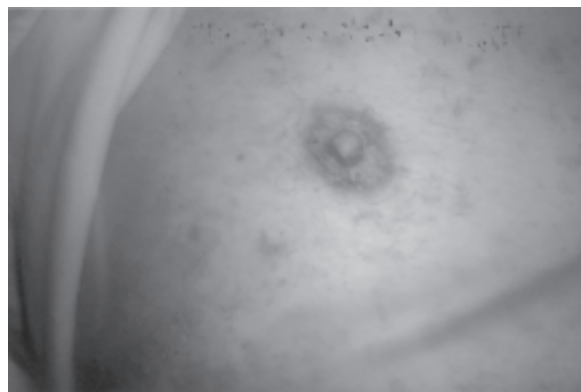


Fig. 1b. Crusts on the nipple.

to treat onchocerciasis. Tolerance is good and side effects are minor and infrequent. Anecdotal case reports have suggested that ivermectin might be an effective treatment in scabies. One randomised, controlled, double-blinded, prospective study compared oral ivermectin to a 1% lindane solution and showed equivalency of both treatments.¹ Another randomised prospective study involving 200 patients showed that systemic ivermectin was more superior to 1% lindane.² In an open-labeled study in which ivermectin was administered in a single dose to 11 otherwise healthy patients with scabies and to 11 patients with scabies who were infected with HIV, ivermectin was an effective treatment for scabies in otherwise healthy patients and in many patients with HIV infection.³ We looked at the efficacy of the combination of oral ivermectin and topical treatment in crusted scabies.

METHODS

This was a retrospective study. Patients diagnosed with crusted scabies in SGH during the study period from December 2002 to October 2003 were included. The diagnoses were all confirmed by positive scrape of scabies. A combined treatment of topical anti-scabetic (malathion, benzyl benzoate, permethrin or combination) and oral ivermectin was given to every patient. Keratolytic ointment (salicylic acid ointment) was applied to crusted lesions. The demographic data, co-morbidity, extent of skin lesions, duration and dosage of ivermectin, concomitant topical treatment were retrieved from the case notes.

RESULTS

Demographic Data

There was a total of 8 patients. The male: female ratio was 3:5. The mean age was 56 (range 35 to 87). Of the patients, there were 6 Chinese and 2 Malays (Table 1).

Home Status

Only one patient was from a nursing home.

Onset of Symptoms to Diagnosis

The mean onset of symptoms to the diagnosis was 3 months and 7 days (range 1 week to 1 year).

History of Recent Admission in the Past 6 Months

Half of the patients had a recent admission in the last 6 months.

Other Medical Problems

All patients had multiple co-morbidities of whom 2 were post-renal transplant patients on immunosuppressive drugs (Table 2). Most of the patients were bed-bound.

Extent of Skin Lesions

Most of the patients had extensive and widespread lesions, such as crusted papules, nodules and plaques. The crusted lesions were found on the hands (Fig. 1a), feet, axillae and nipple (Fig. 1b). One of the patients, who was a post-renal transplant patient, presented as generalised exfoliative dermatitis.

Duration of Treatment

Response to treatment was assessed clinically and microscopically (skin scrape). The duration for the skin scrape to become negative ranged from 4 to 39 days (mean 16.4 days).

Dosage

Three patients were negative in their skin scrape after one dose of ivermectin. They were either discharged before the second dosage was given or their condition clinically and microscopically improved. The rest of

the patients who had clinically active lesions or were scrape positive were given at least 2 doses.

The 2 renal transplant patients were given 3 doses before clinical improvement and negative skin scraping. The dosage ranged from 12 to 27mg. This represented a dosage of 260 to 400mcg/kg body weight. The higher dosage was given to the renal transplant patient with generalised exfoliative dermatitis in the last dosage. The higher dosage cleared up the scabies clinically and microscopically.

DISCUSSION

Crusted scabies poses a problem in the treatment of scabies. These patients have heavy load of mites and are bed-bound. Many patients are immunocompromised. These pre-morbid conditions may also be associated with neglect or difficulty in seeking treatment. These factors probably predispose these patients to crusted scabies.

Hospitals and nursing homes are known to be sources of infestation in bed bound patients. Half of the patients in this study had recent admission to hospital in the preceding 6 months. One of the patients was in a nursing home.

There is often a delay of onset of symptoms and diagnosis in crusted scabies. In this study, we found that half of the patients had symptoms for 1 month or more before the diagnosis of crusted scabies was made. Three patients had symptoms for 3 months or more.

Since patients are bed-bound, there are special problems in administration of topical treatment and treatment of clothing, restraints, bed linen, plaster cast and foot cushions. Topical treatment of crusted scabies in these patients may be associated with the following problems. Part of the infested area may be inadvertently omitted as it is relatively difficult to properly apply treatment, especially under a plaster cast and for patients with dementia, contracture or muscle spasticity. Compliance may also be a problem. Thus, we can anticipate that it would not be easy to eradicate the scabies mites from patients with crusted scabies. Oral treatment with ivermectin offers some advantages and overcomes some of the above problems.

Ivermectin is a member of the avermectin class of broad-spectrum antiparasitic agents. It is isolated from fermentation of *Streptomyces avermitilis* broth. It has a high affinity for the glutamate-gated chloride ion channels that occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of

the cell membrane to chloride ions and inhibition of synaptic transmission. This, in turn, leads to neuromuscular paralysis of the parasite, resulting in the death of the parasite. Ivermectin may also interact with other ligand-gated chloride channels, such as those gated by neurotransmitter gamma-aminobutyric acid. The safety of ivermectin is attributed to the fact that mammals do not have glutamate-gated chloride channels and it has low affinity for mammalian ligand-gated chloride channels. In human beings, peak levels of ivermectin in plasma are achieved within 4 to 5 hours after oral administration. The drug is extensively converted by hepatic CYP3A4 to at least 10 metabolites.⁴ Virtually no ivermectin appears in human urine. Extremely low levels can be found in the brain, even though ivermectin would be expected to penetrate the blood-brain barrier on the basis of its lipid solubility. However, studies in transgenic mice suggest that a P-glycoprotein efflux pump in the blood-brain barrier prevents ivermectin from entering the central nervous system (CNS).⁵ This and the limited affinity of ivermectin for CNS receptors may explain the paucity of CNS side effects and relative safety of this drug in human beings. Because of its effects on gamma-aminobutyric receptors in the CNS, ivermectin is contraindicated in conditions associated with an impaired blood-brain barrier such as meningitis. Caution also is advised about coadministration of ivermectin with other drugs that depress CNS activity. Since ivermectin is metabolised in the liver, precaution should be exercised in patients with liver impairment. It is not absolutely contraindicated in liver impairment, however it may cause AST or ALT elevation.

Ivermectin has not been approved in children under 5 years of age and in pregnant women, but both populations undoubtedly have been exposed to the drug during mass treatment programmes. Lactating women taking the drug secrete low levels in their milk, the consequences for nursing infants are unknown.⁶ Pregnant women should not receive ivermectin because of teratogenic effects seen in animals (at near-toxic doses). Thus, ivermectin is not recommended for pregnant women, lactating women or children under 5 years of age.

There has been a report of increased risk of death associated with ivermectin use in elderly patients.⁷ This case-control study matched case by age and gender, but did not take into consideration any concurrent conditions or other confounding factors that may have influenced the mortality in these elderly patients. Thus, the association described may have been due to contributing factors that were not addressed in the data

analysis. Subsequent reviews of the Barkwell data, a separate retrospective case control study, and retrospective outcomes studies have shown no association with increased mortality in the elderly.⁸⁻¹¹ Clinicians should consider the infrequent and conflicting reports in this area when using ivermectin in elderly patient populations.¹²

Combination oral ivermectin and topical benzyl benzoate solution was more effective than either agent alone in the treatment of crusted scabies in an open study of 30 HIV-positive patients.¹³ Combination treatment with topical anti-scabetic agent and keratolytic agent is recommended because ivermectin cannot penetrate crusts sufficiently. The dosage of ivermectin is 200 or 400mcg/kg body weight. Ivermectin is not ovicidal. A second dose administered after 1 to 2 weeks is aimed at interrupting the typical life cycle of the mite. Larvae usually emerge with 72 hours after eggs being laid. They mature and reproduce for approximately 2 weeks. The second dose would aim to interrupt the mite's life cycle at the maturation process.

There are certain advantages to using ivermectin. It is administered orally and thus is distributed systemically. It can overcome the difficulty of administering topical treatment. It does not have the side effect of local irritation of topical therapy. However, it is relatively more expensive. Scabies are at present an unlicensed indication for ivermectin. It was approved in France on 28 September 2001 for treating *Sarcoptes scabiei* var. *hominis* infestation after clinical diagnosis and/or parasitological examination.

There is concern that widespread use of ivermectin in scabies may result in ivermectin resistance in sarcoptes that may spread to other parasites. There are two mechanisms of resistance. Firstly, resistance may result from alteration of P-glycoprotein, which is a membrane protein that actively transports across cell membranes.¹⁴ Secondly, alterations of chloride channel receptor may decrease the organism's responsiveness to ivermectin therapy.¹⁵ Resistance to ivermectin has been documented in horses, sheep, and goats after almost 20 years of extensive use. So far, there have been no cases of cross-resistance with ivermectin and no resistance has been reported in humans to date.¹⁶

In our group of patients with crusted scabies, a combination treatment of ivermectin, topical keratolytic agent and rotation of topical anti-scabetic agent was used. The results were encouraging. Three of the 8 patients clinically improved and were negative in skin scrapes after one dose of oral ivermectin. The

2 renal transplant patients needed 3 doses of oral ivermectin — one of them needed the higher dosage in the last dose.

We recommend the following guidelines in the treatment of patients with crusted scabies or resistant scabies:

1. Oral ivermectin is to be administered at 200 or 400 micrograms/kg body weight. Two doses are to be given 1 to 2 weeks apart.
2. Topical anti-scabetic treatment — benzyl benzoate, malathion or permethrin (in rotation if necessary) is to be administered in combination with oral ivermectin.
3. Topical keratolytic agent is to be administered to crusted lesions before initiation of treatment or during treatment with oral ivermectin and topical anti-scabetic treatment.
4. Attention is to be paid to the scalp, nails and all crusted lesions.
5. Patient is to be monitored clinically and microscopically until improvement as shown by clinical improvement and negative skin scrapes.
6. Bed linen, clothing, restraint and other appliances are to be changed daily.
7. Contacts are to be treated.

CONCLUSION

Crusted scabies is a management problem due to multiple co-morbidities of patients with impaired immunity and difficulty in application of topical treatment. The combination of oral ivermectin, topical anti-scabetic agent and keratolytic agent offers a satisfactory solution to crusted scabies. This is a study of a small group of patients. More research is needed on the dosage of ivermectin and its application to uncomplicated scabies.

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