

Guidelines for the outpatient treatment of acute symptomatic pulmonary histoplasmosis in cavers

To the Editor: The above paper (published in the *South African Journal of Sports Medicine* 2002; 9 (1): 3-6), not listed in Pubmed by 11 September 2002, came to my recent attention when it was reprinted without acknowledgement in the *Bulletin of the South African Speleological Association*.¹ The author reports his management of acute benign pulmonary histoplasmosis acquired in Gauteng, in presumably immune competent patients, using the anti-fungal drug itraconazole. He compares his treatment of 50 patients using itraconazole with an unstated number of American patients who were treated symptomatically. We are not told if the patients were matched for age, ethnicity, occupation, gender, mass, socio-economic status and smoking habits.

The author concludes that we should treat with 'itraconazole (Sporanox, Janssen-Cilag) 200 mg, two tablets daily for 10 days (total daily dose 400 mg)'. However, in South Africa Sporanox comes in 100 mg capsules.⁹ This misinformation may well confuse patients, and those doctors who do not check their formularies.

The author incorrectly states that, 'There have been no South African studies on the treatment of cavers', and that, 'No South African studies have monitored patients after receiving symptomatic treatment only'. He cites an impressive list of references, mainly from American literature, but he, you and your referee(s) have overlooked the work done on cave explorers' histoplasmosis in the former Transvaal,^{13,15,18} in the Northern Cape² and in the southern Cape.

The author continues that no calcification was seen on repeat chest X-ray after a month. This is to be expected, because calcification is always delayed to a greater or lesser extent. Various authorities give delays of 9 months in children and 2 years in adults,¹⁶ and for adults 10 months,¹⁴ 'several years'¹⁷ and between 5 and 10 years.¹⁰ Therefore, in the absence of clinical evidence of complications, repeat chest X-rays are not indicated.

For many years we in the Cape believed that we had no histoplasmosis, and attributed that to the lower altitude and more southerly latitude which were unfavourable for the propagation of *Histoplasma capsulatum*. Following the 1977 outbreak from a guano cave in the De Hoop nature reserve east of Bredasdorp,⁸ we now know that this is incorrect. A decade after the 1977 incident all but two of the patients were recalled. All had long since made complete clinical recoveries, but most had asymptomatic pulmonary calcification.¹² In 1987 there was a further outbreak from that cave. Five adults got acute benign pulmonary histoplasmosis; the accompanying 12 schoolchildren and 3 speleologists had no clinical evidence of the infection. It is interesting to note that time to recovery varied from 3 weeks in the only Cape patient who has received 'anti-fungal treatment', to 8 weeks.³ We have also had an outbreak from caves north of Oudtshoorn.⁴ Our experience has led us to recommend symptomatic treatment for immune competent patients.⁶

Indeed, the manufacturer of Sporanox admits that, 'proof

of efficacy is limited', and continues that the drug has been used for treatment of unstated varieties of histoplasmosis for a median duration of 8 months (Sporanox package insert dated 25 July 1997). This long period of treatment strongly suggests that acute benign pulmonary histoplasmosis is not a manufacturer's recommended indication for the use of itraconazole. The author's paper confirms this conclusion.

Having discussed the scientific shortcomings of the author's paper, we must now consider the ethical and economic aspects. I have serious doubts about the propriety of undertaking clinical trials in which the patients and/or their funders are required to pay for unnecessary lung function tests¹¹ (between R28 and R89 each according to the tariff used) and repeat chest X-ray (between R157 and R325 according to the tariff used).

The author concludes that his patients, treated with itraconazole 400 mg daily for 10 days, averaged 8.2 days off work, compared with 8.8 days in the American controls, i.e. a saving of 0.6 days! The blue book cost of itraconazole 400 mg daily x 10 is R1 578, or R2 630 per day saved. It is impossible to justify this expenditure on the treatment of a disease which is, by definition, benign. I have made this point previously, in a different context for the same disease, and concluded by saying that, 'Much is being said and written at present about the high cost of medical treatment. If the profession itself does not take urgent steps to curb such over-servicing, others will do it for us'.⁵

I apologise for the delay in bringing this to your attention. The paper under discussion came to my attention in December 2002, just before the inevitable year-end holiday disruptions. This was followed by my visit to India in January 2003, having been invited to lecture on histoplasmosis.⁷

Despite the above shortcomings of his paper, I congratulate the author on his education programme, and on the reduction of the numbers of cases of acute benign pulmonary histoplasmosis in Gauteng.

S A Craven

who declares his relevant various interests although he writes in his private capacity:

Vice-President: SA Speleological Association

General medical practitioner: Wynberg, Cape

Honorary Lecturer: Department of Family Medicine, University of Cape Town

National Councillor: SA Medical Association

Director: Cape Primary Care Holdings (Pty.) Ltd.

Trustee: Profmed Medical Aid Fund

1. Branfield A. Guidelines for the outpatient treatment of acute symptomatic pulmonary histoplasmosis in Cavers. *Bulletin of the South African Speleological Association* 2002; 37: 32 - 6.
2. Craven SA. Histoplasmosis - a possible outbreak in the northern Cape Province. *S Afr Med J* 1981; 60: 125.
3. Craven SA. Acute benign pulmonary histoplasmosis - the third known out-

- break in the Cape Province. *S Afr Med J* 1990; **77**: 376.
4. Craven SA. Acute benign pulmonary histoplasmosis - comparative costs of management. *S Afr Med J* 1992; **81**: 624.
 5. Craven SA. Acute benign pulmonary histoplasmosis - comparative costs of management. *S Afr Med J* 1992; **81**: 624.
 6. Craven SA. Acute benign pulmonary histoplasmosis. *Hospital Update* (South African edition) 1994; **4**: 67 - 70.
 7. Craven SA. Acute Benign Pulmonary Histoplasmosis - A Review. International Conference on Chest Diseases and Allied Sciences, 12 - 14 January 2003, India Habitat Centre, New Delhi. Souvenir and Abstracts: 54.
 8. Craven SA, Benatar SR. Histoplasmosis in the Cape Province A report of the second known outbreak. *S Afr Med J* 1979; **55**: 89 - 92.
 9. Gibbon CJ, ed. *South African Medicines Formulary*. Cape Town: South African Medical Association, 2000: 274-5.
 10. Goodwin RA, Des Prez RM. State of the art histoplasmosis. *American Review of Respiratory Disease* 1978; **117**: 929 - 56.
 11. Gugnani HC. Histoplasmosis in Africa: A Review. *Indian J Chest Dis Allied Sci* 2000, **42**: 271 - 7.
 12. Hall CM, Craven SA. Long-term follow-up of histoplasmosis. *S Afr Med J* 1994; **84**: 365 - 6.
 13. Kaye J, Murray JF. Histoplasmosis — the radiological features of the benign pulmonary form in S Africa. *Medical Proceedings* 1964; **164**: 176 - 83.
 14. Loosli CG, Grayston JT, Alexander ER. Epidemiological studies of pulmonary histoplasmosis in a farm family. *American Journal of Hygiene* 1952; **55**: 392 - 401.
 15. Murray JF. Benign pulmonary histoplasmosis (cave disease) in South Africa. *S Afr Med J* 1957; **31**: 245 - 53.
 16. Procknow JJ. Pulmonary histoplasmosis in a farm family: fifteen years later. *American Review of Respiratory Disease* 1967; **95**: 171 - 88.
 17. Schwarz J, Baum GL. Pulmonary histoplasmosis. *Semin Roentgenol* 1970; **5**: 13 - 28.
 18. Wolpowitz A, van Eeden J. Histoplasmosis - cave disease. *S Afr Med J* 1963; **37**: 1002 - 5.

Dr Branfield replies: Thank you Dr Craven for your interest and comments. It should firstly be stressed that this paper was generated in private practice without access to medical libraries or research facilities. The article has still not been listed in Pubmed, Medline, or Ovid, nor has any other South African article on the treatment of acute symptomatic pulmonary histoplasmosis in cavers. I restate that to the best of my knowledge when this article was published I knew of no South African articles that specifically dealt with the treatment of symptomatic cavers. In a recent search of Pubmed and Medline none of publications referenced in your letter were found. I searched under both 'Histoplasmosis' and 'caver' It shows that the reseach tools available to me were and remain limited. I apologise for this. The comments as regards the capsule strength are valid. The capsule used

was 100 mg of itraconazole and not 200 mg as stated. This makes the dose used 200 mg and not 400 mg. This has important cost implications later on as the calculated costs are half those stated and similar to a 10-day course of an antibiotic, e.g. a macrolide that may be used in another form of atypical pneumonia. I agree that the dosage is confusing and I will attempt to address this. The patients were not matched with the patients in the American study as regards age, sex, etc. Your comments on calcification are valid. The purpose of the X-rays on follow-up was to show resolution of acute radiological changes and no long-term follow-up X-rays, e.g. after 9 months or longer, were done in this study.

The rest of the letter deals with ethical and economic aspects. The cost of the medication can be recalculated as the dosage has been corrected. The lung function testing showed a documented improvement in function and is in my opinion justified. The follow-up X-ray showed resolution or improvement in acute radiological change and is also justified. Would a follow-up X-ray and lung function testing in other forms of atypical pneumonia also be unjustified? Why do the ethics relating to histoplasmosis differ from those of other atypical pneumonias? The other cost that has not been mentioned is that these patients have often been treated on one or more courses of inappropriately prescribed antibiotics before the final diagnosis is made. These patients were excluded from the study (see inclusion criteria) but have been treated by me on occasion. The remarks about cost-effective medicine being a concern are valid but I feel that pointing a finger at me is not justified as my own track record of keeping medical expenses down as a priority since entering private practice in 1988 has never been questioned before. The patients treated were all symptomatic. Treatment has not been advocated in the asymptomatic. Acute symptomatic pulmonary histoplasmosis is a benign condition but then so are most conditions seen in general practice. Should we adopt the attitude of not treating histoplasmosis in this form because it is benign? Surely the same approach must then apply to all other benign conditions? Is our role as doctors not to alleviate pain and suffering in our patients? What I have tried to do is to offer patients an alternative to symptomatic treatment only over a protracted period of time. I have used the limited resources that I have available away from research facilities and financial grants. The incidence of acute symptomatic pulmonary histoplasmosis has decreased significantly since this study was initiated. Thank you for pointing this out.