Eur J Clin Pharmacol (2000) 56: 437–438

LETTER TO THE EDITORS

E. N. Shu · E. O. Onwujekwe · P. O. Okonkwo

Do alcoholic beverages enhance availability of ivermectin?

Received: 7 July 1999 / Accepted in revised form: 14 February 2000

Key words Ivermectin · Alcoholic beverages · Filariasis

Ivermectin is now the sole drug for the treatment of lymphatic filariasis and onchocerciasis. Lymphatic filariasis causes suffering to 120 million people and threatens 1100 million more in 73 countries. Meanwhile, 18 million people are infected with onchocerciasis, 99% of whom live in Africa [1]. The burden caused by these diseases was estimated as four million and 884,000 disability-adjusted life years (DALYs) for lymphatic filariasis and onchocerciasis, respectively [2]. Ivermectin is relatively safe [3], with the incidence of side effects decreasing markedly after the first year of ingestion [4].

Alcohol restriction during drug distribution programmes is normally resisted by the community. In the case of ivermectin, the community-wide distribution programme's initial restriction was for all drugs affecting the central nervous system because of the association of the drug with gamma-aminobutyric acid (GABA) receptors [5]. In our own distribution programme among rural dwellers in Oji River in south eastern Nigeria within the last 9 years [6], we often encountered indiscriminate ingestion of alcoholic beverages. Community-based distributors (CBDs) who were rigid in enforcing this restriction encountered hostility from the community.

However, some members of the community reported anecdotes of "potent" effects of the drug after ingestion of the local alcoholic beverage, palm wine. Indeed the more dramatic the side effects of ivermectin were, the more these subjects extolled its "power". Thus, the few cases of ataxia and postural hypotension encountered were in individuals who had concurrently taken the local alcoholic beverage on the day of ivermectin administration [7]. On the one hand, alcohol restriction could hurt compliance and acceptability of ivermectin while, on the other, may contribute to real or imagined side effects or "potency". We therefore report here, our studies on co-administration of an alcoholic beverage and ivermectin with the aim of investigating the influence of the former on plasma ivermectin concentration.

Plasma ivermectin concentrations were measured in 20 healthy, non-smoking male volunteers, aged 22–32 years and weighing between 65 kg and 70 kg. The subjects were not on any form of drug and were advised to keep away from alcoholic drinks for the 2 weeks prior to the investigation. One group of ten (the study group) received ivermectin (150 μg/kg) as a single oral dose with 750 ml beer (Star brand, Nigeria Brewery Ltd), while the rest (the control group) received an equivalent dose of the drug with 750 ml water. Star beer contains 4.5% (v/v) alcohol. The subjects in the study group received an average of 400 mg alcohol per kilogram body weight. Blood samples were taken pre-dose and at 1, 3 and 4 h following ivermectin administration.

Ivermectin was analysed using high-performance liquid chromatography (HPLC) following derivatisation and fluorescent detection, as previously described [8, 9].

The plasma ivermectin concentrations in both study and control subjects are represented in Table 1. During the period of study, plasma ivermectin concentrations were significantly higher when co-administered with alcoholic beverage than with water. Our subjects were fasted prior to the beginning of the study, hence the early appearance of peak plasma ivermectin concentrations within 3 h. There were no side effects in either study or control subjects. It has been reported that the intensity and incidence of adverse events is related to pre-treatment microfilarial load [10]. However, ivermectin is toxic to beagle dogs, premature infants, adult epileptics and those with other central nervous system disorders.

E. N. Shu (✉) · E. O. Onwujekwe · P. O. Okonkwo
Department of Pharmacology and Therapeutics,
College of Medicine, University of Nigeria,
Enugu Campus, PMB 01129, Enugu, Nigeria
e-mail: obionwuj@infoweb.abs.net
Tel.: +234-42-259569; Fax: +234-42-259569

Table 1 Plasma ivermectin concentrations (ng/ml) in onchocerciasis patients, administered ivermectin (150 μg/kg) concomitantly with either alcoholic beverage or water

Period	Alcoholic beverage ($n = 10$)		Water ($n = 10$)	
	Mean (SD)	Range	Mean (SD)	Range
1 h	66.3 (12.1)	21.5–84.8	*44.0 (9.8)	22.3–59.4
3 h	109.0 (17.2)	63.0–144.8	*67.5 (11.9)	60.6–93.6
4 h	97.2 (14.4)	47.9–128.0	*58.7 (11.3)	29.2–80.1

* Significantly different to value of alcoholic beverage consumption, $P < 0.01$

Ivermectin is thought to potentiate the release and binding of GABA, the neurotransmitter primarily responsible for neural inhibition in man [11]. Other high-affinity GABA and ligand-gated chloride channels are activated by ivermectin in nematodes, arthropods and crustacea [12]. Also, glutamate-gated chloride channels are found exclusively in invertebrates [13]. An acute ingestion of alcohol, however, raises plasma levels of GABA in a healthy man [14]. No previous study on the influence of alcohol on bioavailabilty of ivermectin has been done. The most similar experiment was one where ivermectin in alcoholic solution was shown to have approximately twice the systemic availability as tablets, capsules and oral solutions [15].

Beer contains other components besides alcohol. However, alcohol is the main active component affecting the central nervous system side effects observed, when co-ingested with ivermectin [7]. Further studies should be done to confirm the findings of this study.

References

1. WHO (1997) Tropical disease research, progress 1995–96. Thirteenth Programme Report. World Health Organization, Geneva
2. WHO (1996) Investing in health research and development. Report of the Ad Hoc committee on health research relating to future intervention options. World Heath Organization, TDR/Gen/96.1, Geneva
3. Pacqui M, Muñoz B, Greene BM, Taylor HR (1991) Community-based treatment of onchocerciasis with ivermectin: safety, efficacy, and acceptability of yearly treatment. J Infect Dis 163: 381–385
4. Njoo FL, Stilma JS, Van der Lelij (1992) Effects of repeated treatment in onchocerciasis. Doc Ophthalmol 79: 261–267
5. Pong SS, Wang CC, Fritz LC (1980) Studies on the mechanism of action of avermectin B_{1a}: stimulation of release of gamma-aminobutyric acid from rain synaptosomes. J Neurochem 34: 351–358
6. Okonkwo PO, Akpa A, Ihekwaba A, Nwagbo D, Umeh F, Adibua S, Ezike V, Ogbuokiri J (1991) Studies on onchocerciasis in forest-savannah mosaic areas of Nigeria. 1. Investigations in Gbaragu Oji River. Ann Trop Med Parasitol 85: 617–623
7. Chijioke CP, Okonkwo PO (1992) Adverse events following mass ivermectin therapy for onchocerciasis. Trans R Soc Trop Med Hyg 86: 284–286
8. Klotz U, Ogbuokiri JE, Okonkwo PO (1990) Ivermectin binds avidly to plasma proteins. Eur J Clin Pharmacol 39: 606–608
9. Shu EN, Okonkwo PO (2000) Pharmacokinetics of ivermectin in rabbit. West Afr J Biol Scs (in press)
10. Njoo FL, Belling GAC, Oocting J, Vetter JCM, Stilma JS, Kijlstra A (1993) Concurrent parasitic infections in onchocerciasis and occurrence of adverse reactions after ivermectin treatment. Am J Trop Med Hyg 48: 652–657
11. Wang CC, Pong SS (1982) Actions of ivermectin B1a on GABA nerves. Prog Clin Biol Res 97: 377–395
12. Turner MJ, Schaeffer JM (1989) Mode of action of ivermectin. In: Campbell WC (ed) Ivermectin and abamectin. Springer, Berlin Heidelberg New York
13. Cully DF, Vassilatis DK, Liu KK, Paress PS, Van der Ploeg LH, Schaeffer JM, Arena JP (1994) Cloning of an avermectin-sensitive glutamate-gated chloride channel from *Caenorhabditis elegans*. Nature 371: 707–711
14. Bannister P, Levy L, Bolton R, Losowsky M (1988) Acute alcohol ingestion raises plasma levels of GABA in healthy men. Alcohol Alcoholism 23: 45–48
15. Edwards G, Dingsdale A, Helsby N, Orme MLE, Breckenridge AM (1988) The relative systemic availability of ivermectin after administration as capsule, tablet and oral solution. Eur J Clin Pharmacol 35: 681–684