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A qualitative analysis of seven ivermectin formulations in South Africa

Q E Bhorat, MB BCh, MSc; **A E Bhorat,** MB BCh, MCFP (SA), FRACGP

Independent researchers, Soweto Clinical Trials Centre, Johannesburg, South Africa

Corresponding author: *Q E Bhorat (qeb@sowetoctc.co.za)*

Some South African (SA) healthcare practitioners are promoting the prescription and use of products claiming to contain ivermectin for the treatment and/or prevention of COVID-19 in SA. This study qualitatively analysed seven samples of ivermectin formulations (5 tablet and 2 capsule formulations) being sold in SA for human use. The samples were analysed using a high-performance liquid chromatography instrument connected to a Sciex X500R quadrupole time-of-flight high-resolution mass spectrometer. The study found that all the samples had both the major homologues of ivermectin (B1a and B1b) and also that 4 out of the 5 tablet formulations tested had at least one additional undeclared active pharmaceutical ingredient.

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Ivermectin is a member of the avermectin class of broad-spectrum antiparasitic drugs indicated for the treatment of onchocerciasis and intestinal strongyloidiasis in human beings.[1] It has recently been proposed as a medication for the prophylaxis and treatment of COVID-19 infections.[2,3]

Some South African (SA) healthcare practitioners are promoting the prescription and use of products claiming to contain ivermectin for the treatment and/or prevention of COVID-19 in SA.[4] There is also strong social media advocacy for its use. The current scientific evidence on the efficacy of ivermectin in the treatment and/or prophylaxis of COVID-19 remains equivocal,[5] with recommendations that additional quality data are required before its use can be recommended or not.[6]

To date, there is no formulation of ivermectin registered or approved for human use in SA.[7] The ivermectin formulations being used to manage COVID-19 in SA are principally from three sources: veterinary preparations, which are widely available as intravenous formulations for injection; compounding pharmacies; or illegal importation. Illegal importation of ivermectin pharmaceutical formulations has become a significant source of the ivermectin being sold, dispensed and used in SA.[8,9] This illegal and unregulated sourcing of ivermectin raises questions around the quality and the content of the ivermectin being prescribed and used.

The objective of this study was to analyse and compare seven different ivermectin formulations currently being used in SA, which were sourced through purchases from suppliers and donations by suppliers/users.

Methods

Ivermectin formulations were sourced and, based on availability, supplies were secured from various suppliers over a period of 3 weeks (12 January - 3 February 2021). Suppliers were contacted based on information obtained from word of mouth and social media information. Five different tablet formulations and 2 different capsule formulations of ivermectin were sourced and secured. Four of the 5 samples (samples B - E) were received as a single foil blistered card without a box. Sample A was received in a box comprising 15 foil blister cards with two tablets each. Samples F and G were received as loose capsules in a transparent sealed plastic bag. The details and description of these samples are set out in Tables 1 and 2, respectively.

These samples were received in Johannesburg and stored at room temperature, protected from light, until being packaged in a sealed plastic container on 3 February 2021. All 5 of the tablet formulations, sealed in their original individual foil blisters, were placed in sealable plastic bags, while the 2 capsule formulations were placed loose in sealable plastic bags. Two individual tablets/capsules of each of samples A, B, C, D, E and F, plus one capsule of sample G, were couriered on 4 February (time 17h41) to the University of Cape Town (UCT) Toxicology Laboratory, Division of Clinical Pharmacology, Groote Schuur Hospital, Cape Town, and received on 5 February (time 16h00). No evidence of any tampering with the package was reported by either the courier or the recipient.

The UCT Toxicology Laboratory (an academic research laboratory) prepared the samples for analysis according to their drug screen protocol using a high-performance liquid chromatography (HPLC) instrument (Exion; SCIEX, USA) connected to an X500R quadrupole time-of-flight (QTOF) high-resolution mass spectrometer (SCIEX, USA). The data acquired for each sample were processed against the UCT Toxicology Laboratory's drug screen database of over 700 compounds.

Results

The qualitative analysis results of the seven samples are presented in Table 3.

Discussion

All the samples tested were shown to have both the major homologues of ivermectin (B1a and B1b). As this was purely a qualitative analysis, the actual amounts of ivermectin were not determined. A quantitative analysis to determine the exact amounts of ivermectin in another batch of ivermectin formulations is currently being executed.

This study found that 4 of the 5 tablet formulations tested had at least one additional undeclared active pharmaceutical ingredient (API). The number of additional undeclared APIs found ranged

Table 1. Sample details

Sample and labelled name	Labelled country of manufacture	Batch number	Manufacture date	Expiry date	Labelled composition	Price per 10 tabs/caps (ZAR)
A: Ivery12	India	2065	Dec 2020	Nov 2023	Ivermectin IP 12 mg, excipients q.s.	73.33
B: Iverwon-12	India	LMT200619	Sep 2020	Aug 2022	Ivermectin IP 12 mg, excipients q.s.	480.00
C: Spimect-12	India	SPTG-20453	Sep 2020	Aug 2022	Ivermectin IP 12 mg, excipients q.s.	500.00
D: Iveractin12	India	DLT-6033	Oct 2020	Sep 2022	Ivermectin IP 12 mg, excipients q.s.	1 000.00
E: Biomec12	Bangladesh	1EO622	Unknown	Unknown	Ivermectin BP 12 mg, excipients q.s.	Donated
F: Ivermectin 18 mg	South Africa	2012366	Jan 2021	Dec 2021	Ivermectin 18 mg	Donated
G: UNK 18 mg	South Africa	Unknown	Unknown	Unknown	Ivermectin 18 mg	Donated

Table 2. Sample descriptions

Sample and labelled name	Formulation	Package insert	Patient information leaflet	Packaging	Visual inspection
A: Ivery12	Tablet, uncoated	No	No	Box of 30s, foil card of 2s, individually blistered with transparent plastic	Round white tablet, scored
B: Iverwon-12	Tablet, uncoated	No	No	Foil card of 10s, individually blistered with foil	Round tablet
C: Spimect-12	Dispersible tablet, uncoated	No	No	Foil card of 10s, individually blistered with transparent plastic	Round white tablet, scored
D: Iveractin12	Tablet, film coated	No	No	Foil card of 10s, individually blistered with foil	Round tablet
E: Biomec12	Tablet	No	No	Foil card of 10s, individually blistered with foil	Round tablet
F: Ivermectin 18 mg	Capsule, vegetable	No	No	Two capsules in a plastic bag	White capsule
G: UNK 18 mg	Capsule	No	No	One capsule in a plastic bag	White capsule

Table 3. Qualitative analysis results of all seven samples

Sample	Ivermectin detected	Other compounds detected
A	Ivermectin (B1a, B1b)	Paracetamol (acetaminophen), dicyclomine
B	Ivermectin (B1a, B1b)	Telmisartan
C	Ivermectin (B1a, B1b)	Paracetamol (acetaminophen), diclofenac, hydroxyzine, mebeverine, nortriptyline, ornidazole, pregabalin
D	Ivermectin (B1a, B1b)	Paracetamol (acetaminophen), clopidogrel, etizolam
E	Ivermectin (B1a, B1b)	None
F	Ivermectin (B1a, B1b)	None
G	Ivermectin (B1a, B1b)	None

from 1 to 7 per tablet. Sample C (Spimect-12) had the highest count of additional undeclared APIs at 7, and sample D (Iveractin12) the second-highest count at 3. Sample A (Ivery12) had 2 additional undeclared APIs, while sample B (Iverwon-12) had 1 additional undeclared API. Sample E (Biomec12) was the only tablet formulation that had no additional undeclared APIs.

Both the locally compounded capsules (samples F and G) had no additional undeclared APIs. Sample F was supplied with a separate label indicating the batch number and manufacture and expiry dates, but sample G was not supplied with any of this information.

None of the seven ivermectin formulations had a package insert or a patient information leaflet.

The ivermectin tablet formulations all had labelling claiming manufacture outside SA's borders and have therefore been illegally imported into SA and dispensed/sold/used as a potential treatment for COVID-19, thereby bypassing South African Health Products Regulatory Authority (SAHPRA) registration and any other SA quality control process or check. Both the ivermectin capsule formulations were compounded in SA.

All four of the ivermectin tablet formulations (samples A - D) labelled as manufactured in India had at least one additional undeclared API. The one tablet formulation (sample E) that was apparently manufactured in Bangladesh had no additional undeclared API; however, it had no manufacture or expiry date on the foil card.

The average price paid for 10 ivermectin tablets (samples A - D) was ZAR513.33. Samples E, F and G were donated towards this study.

A total of 10 different undeclared APIs were identified by the HPLC QTOF analysis. Acetaminophen (found in samples A, C and D) is an analgesic and antipyretic.[10] Dicyclomine (found in sample A) is an antimuscarinic drug that also has antispasmodic action.[11] Diclofenac (found in sample C) is a non-steroidal anti-inflammatory drug used for the relief of pain and inflammation.[12] Hydroxyzine (found in sample C) is a histamine H_1-receptor antagonist with sedative, anxiolytic and anti-emetic properties.[13] Mebeverine (found in sample C) is an antispasmodic with direct action on the smooth muscle of the gastrointestinal tract.[14] Nortriptyline (found in sample C) is a tricyclic antidepressant with mild sedating effects.[15] Ornidazole (found in sample C) is a nitroimidazole with the antimicrobial actions of metronidazole.[16] Pregabalin (found in sample C) is an antiepileptic used in the treatment of partial seizures, generalised anxiety disorders and fibromyalgia with the most common adverse events being somnolence and dizziness.[17] Clopidogrel (found in sample D) is an inhibitor of platelet aggregation.[18] Etizolam (found in sample D) is a short-acting benzodiazepine derivative used for the short-term treatment of insomnia and anxiety disorders.[19]

Some of these APIs have properties that may play a clinical role in management of the symptoms of COVID-19 infections. Given the high percentage (57%) of ivermectin formulations shown to have additional undeclared APIs, anecdotal evidence of successful COVID-19 treatment with ivermectin formulations may be confounded by the possible intentional addition of these undeclared medications to target and alleviate COVID-19 symptoms. This may well contribute to the impression of efficacy in ameliorating COVID-19 symptoms, and requires further evaluation and analysis.

The fact that 80% of the ivermectin tablet formulations tested in this study contained undeclared additional APIs that are unknown to both the prescriber and the patient has potential safety concerns for any person who uses these formulations. Potential safety concerns include, but are not limited to, allergies, drug interactions and the side-effect profile of the relevant API.

While ingestion of these products may raise significant potential safety concerns for patients, it may also create consequent legal ramifications for the dispenser and/or prescribing doctor of these unregistered medications. The safety and legal concerns of using unregistered ivermectin formulations for the treatment or prophylaxis of COVID-19 highlighted by this study are therefore important information for both prescribers and patients.

Limitations of this study include that these seven samples may not be representative of all ivermectin medication formulations available in SA. Inter-batch variation within these seven formulations may render this study result less reproducible at a different time point. There remains value in repeating this study at another time point in the future with an increased sample size of ivermectin formulations, to validate the findings of this analysis. A further limitation of this study is that the laboratory utilised for the sample analysis is an academic research laboratory and not accredited by the South African National Accreditation System (SANAS).

Declaration. None.

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