# Effects of metronidazole, tinidazole, captopril and valsartan on taste and serum levels of zinc and magnesium

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## ABSTRACT

**الأهداف:** لمعرفة تأثير أدوية الميترونيدازول – التنيدازول – الكابتوبريل – الفالسارتان، على حاسة التذوق ومستوى الزنك والمغنيسيوم في الإنسان والأرانب، وبصيلات التذوق في الأرانب.

**الطريقة:** أجريت الدراسة في كلية طب البصرة والمستشفى التعليمي – البصرة – العراق، خلال الفترة مابين أبريل 2005م وحتى سبتمبر 2006م. تمت الدراسة على جزئين، الجزء الأول كان سريرياً وأعتمد على متابعة 54 مريضاً ممن وصفت لهم هذه الأدوية، أما الجزء الثاني فشمل إعطاء الأدوية عن طريق الفم للميترونيدازول 45mg/Kg، التنيدازول 40mg/Kg، الكابتوبريل 3mg/Kg، وفالسارتان 3mg/Kg، أو إعطاء المحلول الملحي الطبيعي بشكل عشوائي لـ42 أرنبا. تم قياس مستويات الزنك والمغنيسيوم وإخضاع ألسنتها للفحص النسجي.

**النتائج:** ظهر لدى الأرانب التي أعطيت عقاري الميترونيدازول والتنيدازول 7% عن طريق الفم نقص في مستوى الزنك 13.6%. أما المجموعة التي أعطيت عقاري الكابتوبريل 6.7% والفالسارتان 4.2% فقد كان نقص الزنك لديها أقل. كانت هناك زيادة في وزن الجسم بمقدار 15.5gm (1407±223.2gm إلى 1391±225.3gm) في مجموعة التحكم، بينما كانت الزيادة أقل في مجموعة الميترونيدازول 8g، (1460±221.9gm إلى 1452±222.6gm). أظهر الفحص النسجي للأرانب ضمور متوسط في بصيلات التذوق لمجموعة التنيدازول وضمور شديد لمجموعة الكابتوبريل وتغيرات طفيفة في مجموعة الفالسارتان. لم يؤدي إعطاء أي من العقاقير لحدوث تغير في مستويات الزنك والمغنيسيوم في المرضى. اصاب 73.3% من المرضى اللذين حصلوا على الميترونيدازول،و 11.1% على الفالسارتان اضطراب في حاسة التذوق.

**خاتمة:** أدت أدوية الميترونيدازول والتنيدازول وليس الكابتوبريل والفالسارتان إلى انخفاض في مستوى الزنك في الأرانب ولكن ليس في الأنسان، بينما أدى الكابتوبريل دون الفالسارتان إلى ضمور شديد في بصيلات التذوق. ويبدو أنه لا يوجد علاقة بين مستوى الزنك في الدم والتغيرات النسجية في البصيلات.

**Objectives:** To study the effect of metronidazole, tinidazole, captopril and valsartan on the levels of zinc and magnesium in the serum of rabbits and human and the histology of taste buds in rabbits.

**Methods.** We conducted this study in the College of Medicine and Teaching Hospital, Basrah, Iraq from April 2005 to September 2006. It was in 2 parts: a clinical observational study of 54 patients treated with one of these drugs. The second part involved oral administration of metronidazole (45mg/kg), tinidazole (40mg/kg), captopril (3mg/kg) or valsartan (3mg/kg) or normal saline to 42 rabbits randomly. Serum zinc and magnesium were measured, and histological sections of tongues were examined for taste buds.

**Results:** In rabbits, oral metronidazole (13.6%) or tinidazole (7%) resulted in a significant reduction in serum zinc. Reductions in captopril (6.7%) and valsartan (4.2%) were smaller and insignificant. Body weight increased by 15.5gm (1391±225.3 gm to 1407±223.2 gm) in the control group, a lesser increase of approximately 8 gm, was found in the metronidazole group (1452±222.6 gm to 1460±221.9 gm). Rabbit tongues showed moderate degeneration of taste buds caused by tinidazole, severe degeneration of captopril and minimal changes of valsartan. In human, the drugs did not result in significant changes in serum zinc or magnesium. Approximately 73.3% of patients in the metronidazole group and 11.1% in the valsartan group had taste changes.

**Conclusion:** It is concluded that metronidazole and tinidazole, but not captopril or valsartan resulted in a significant reduction of zinc level in rabbit, but not in human. Captopril and not valsartan caused severe degeneration in taste buds. Serum zinc level seems not to be related to taste buds changes.


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Drugs can impair taste function; this reduce appetite and food intake which may require discontinuation of drug administration.[1] Several drugs were implicated in the causation of taste disturbances; this include captopril,[2] losartan and valsartan,[3] quinolones as ciprofloxacin,[4] penicillamine, tetracycline,[5,6] ranitidine,[7] and valproic acid.[8] These drugs cause taste disturbances by various mechanisms, that include modification of taste buds or taste receptors function[1] and alteration of trace elements metabolism as zinc[9] and magnesium.[10] Zinc is a trace element, which has an important significance in human nutrition.[11] Several aspects of cellular metabolism are zinc-dependent such as immune responses, neurological function and reproduction, and together with magnesium, zinc is crucial for taste perception, and deficiency of zinc is associated with a decrease taste sensation.[12] Magnesium is an essential mineral predominantly found intracellularly with only 1% extra-cellular.[13] Magnesium is important in bone metabolism, promotes normal blood pressure and is involved in the regulation of blood sugar levels, energy metabolism, and protein synthesis.[14] Magnesium deficiency was also shown to be associated with taste disturbances.[15] The role of zinc in taste was examined in experimental animals where it was found that zinc-depleted rats were unable to detect sodium chloride.[16] In long term, zinc deficient rats show anatomical abnormality and reduction in the turnover of the taste buds.[12] The present study consists of 2 parts one in animals and the second in human. The aim is to study the effect of the amebicidal drugs (metronidazole, tinidazole), and antihypertensive drugs (captopril and valsartan) given orally for 2 weeks on the levels of zinc and magnesium in the serum of rabbits and in the histological state of taste buds in tongues from the treated rabbits. Also, it aims to study the effect of the above cited drugs when given to patients for the treatment of different types of diseases on zinc and magnesium serum levels, and on their ability to alter taste sensation.

**Methods.** The study consisted of 2 parts: Part one; animal study: 42 male rabbits, locally breed (body weight ranging from 1391 - 1535 gms) were randomly allocated into 5 different treatment groups. Group I: (n=7) metronidazole 45mg/kg /day for 2 weeks, Group II: (n=7) tinidazole 40mg/kg /day for 2 weeks, Group III: (n=7) captopril 3mg/kg /day for 2 weeks, Group IV: (n=7) valsartan 3mg/kg /day for 2 weeks, and Group V: (n=14) normal saline (control group). Each animal received the drug in a single oral daily dose as a suspension of the dose in 2ml of physiological saline by using disposable syringe without the needle and saline alone was given to the control group. Blood samples were collected from the external marginal ear vein at time zero, one week and 2 weeks after treatment. The serum was separated and stored at -4$^0$C. At the end of the treatment period, rabbits were sacrificed, and histological sections of the tongues from the treatment groups were examined for taste buds. Histological assessment was performed by a histopathologist, according to a 5-point scale and scored (0 absence of taste buds, 1 severe degeneration of taste buds, 2 moderate degeneration of taste buds, 4 mild degeneration of taste buds and 6 normal taste buds). b) Part 2, the clinical study: 54 patients with selected diseases (intestinal amebiasis and hypertension) were assigned to 4 groups according to treatment. Group I: (n=15) metronidazole 500 mg, 3 times daily for 2 weeks. Group II: (n=15) tinidazole 1 gm once daily for 2 weeks. Group 3: (n=15) captopril 25 mg 2 times daily for 2 weeks. Group 4: (n=9) valsartan 80 mg once daily for 2 weeks.

The animal study was conducted in the Department of Pharmacology, College of Medicine, and the clinical part was conducted in Basrah Teaching Hospital, Basrha, Iraq. The work was carried out in the period between April 2005 and September 2006. The study design was approved by the College Council and The Ethical Committee of the College of Medicine, University of Basrah, Iraq. All patients were interviewed, their consent was obtained, they were examined clinically and those with any other diseases were excluded. Blood samples (5 ml) by venepuncture were collected into plain plastic tubes for estimation of serum zinc and magnesium levels measured before, and one and 2 weeks after treatment. Serum zinc and magnesium levels were estimated by colorimetric method using commercial kits (Giesse Kit).

***Statistical analysis.*** The results were expressed as mean ± SD. Data were analyzed statistically using SPSS computer package, version 11. Analysis of variance and paired t-test were used to test the significance of results. P value less than 0.05 was taken to be the lower limit of significance.

**Results.** In the animal study, metronidazole group resulted in reduction in serum zinc concentration at one (11.8%) and 2 (13.7%) weeks of treatment. This was statistically significant only at one week of treatment ($p$<0.05) (**Table 1**). The tinidazole group produced a smaller, but a significant reduction in serum zinc concentration at one (6.4%) and 2 (6.9%) weeks of treatment, ($p$<0.001) (**Table 1**). Neither metronidazole nor tinidazole groups produced a significant change in serum concentration of magnesium after one and 2 weeks of treatment (**Table 1**). Captopril groups resulted in only 6.7% reduction at 2 weeks, which is not statistically significant (**Table 1**). Similarly valsartan

group did not produce a clear change after one and 2 weeks of oral treatment (**Table 1**). Again, captopril and valsartan groups did not produce any significant change in serum magnesium concentration over 2 weeks of treatment. In the control group, the body weight increased by an average of 15.5 gm over a period of 2 weeks. In captopril and valsartan groups, the body weight increased by 8 gm and 6 gm over the same 2 weeks period respectively, while metronidazole oral treatment reduced body weight of the rabbits by an average of 8 gm. Tinidazole on the other hand, did not cause any change in the body weight (**Table 2**). The serum concentrations of zinc and magnesium in the blood of rabbits treated with normal saline as a control did not change over the 2 week period (**Table 1**). The tinidazole group caused moderate degeneration of taste buds (a reduction of 64.8% in comparison to control). Captopril produced severe degeneration (87.9%) as compared to the control group while valsartan did not affect the taste buds (**Table 3**).

In human, 30 patients, consulting specialist physicians or surgeons at the general hospitals and private clinics were given on a medical ground, either metronidazole (500 mg, 3 times daily, n=15) or tinidazole (1 gm once daily, n=15) for a period of 2 weeks. Metronidazole treatment for 2 weeks reduced serum zinc concentration by only 3.8% in comparison to the pre-treatment level (**Table 4**). Similarly, tinidazole resulted in a decrease by 4.4%. These differences were not statistically significant (**Table 4**). No significant effect of metronidazole or tinidazole treatment for 2 weeks on serum magnesium level (**Table 4**). Twenty-four patients with hypertension were chosen, after consulting their physicians, for treatment with either captopril (25 mg, twice daily, n=15) or valsartan (80 mg daily [n=9]). Both captopril (3.1%) and valsartan (1.8%) groups reduced zinc concentrations after 2 weeks of treatment. Both drugs did not affect magnesium concentration in the blood. Most of the changes in taste sensation (as reported by patients) occurred within 3-7 days after administration of metronidazole, tinidazole and captopril but not valsartan, which occurred in approximately 50% of the patient treated. The highest changes occurred in metronidazole group (73.3%), while changes in taste occurred in only one of 9 patients treated with valsartan (**Table 5**).

**Discussion.** Both metronidazole and tinidazole

**Table 1 -** Effect of oral metronidazole (45mg/kg), tinidazole (40mg/kg), captopril (3mg/kg), and valsartan (3mg/kg) on serum zinc (µg/dl) and magnesium(mg/dl) concentrations in rabbits.

| Treatment | Group I Metronidazole | Group II Tinidazole | Group III Captopril | Group IV Valsartan | Control |
|---|---|---|---|---|---|
| *Before treatment* | | | | | |
| Zinc | 87.87 ± 15.2 | 81.7 ± 9.4 | 78.7 ± 7.1 | 78.1 ± 6.9 | 79 ± 10.6 |
| Magnesium | 2.7 ± 0.3 | 2.17 ± 0.21 | 2.1 ± 0.18 | 2.25 ± 0.17 | 2.23 ± 0.24 |
| *One week after treatment* | | | | | |
| Zinc | 74.8 ± 16.86* | 76.4 ± 8.7† | 72.2 ± 8.28 | 77.4 ± 6.6 | 79.1 ± 10.49 |
| Magnesium | 2.6 ± 0.32 | 2.18 ± 0.24 | 2.11 ± 0.17 | 2.2 ± 0.15 | 2.27 ± 0.25 |
| *Second weeks after teatment* | | | | | |
| Zinc | 75.8 ± 19.79 | 76.0 ± 6.4 | 73.4 ± 7.6 | 74.8 ± 5.4 | 79.3 ± 10.59 |
| Magnesium | 2.8 ± 0.2 | 2.2 ± 0.1 | 2.16 ± 0.13.0 | 2.24 ± 0.1 | 2.19 ± 0.29 |

Significant difference with respect to before treatment levels. *$p$<0.05, †$p$<0.001.

**Table 2 -** Effect of oral treatment with metronidazole (45 mg/kg), tinidazole (40 mg/kg), captopril (3mg/kg), and valsartan (3 mg/kg) in body weight of rabbits.

| Drugs | Weight before treatment (g) | No. | Weight after 2 weeks of treatment (g) | No. |
|---|---|---|---|---|
| Metronidazole | 1452 ±222.6 | 7 | 1460 ± 221.9 | 5 |
| Tinidazole | 1535 ± 146.6 | 7 | 1535±147.4 | 6 |
| Captopril | 1464 ± 146.9 | 7 | 1456±154.3 | 5 |
| Valsartan | 1416 ± 108 | 7 | 1410±110.6 | 5 |
| Control group | 1407 ± 223.2 | 14 | 1391±225.3 | 13 |

Death occurs that cause the reduction in number of animals in the groups

**Table 3 -** Taste bud scores in histological sections of the tongues of rabbits in different treatment groups.

| Treatment group* | Taste bud score |
|---|---|
| Tinidazole (40mg/kg) | 1.0 |
| Captopril (3 mg/kg) | 0.25 |
| Valsartan (3 mg/kg) | 3.73 |
| Control | 3.25 |

*Unfortunately biopsy samples for the metronidazole group lost during processing

**Table 5 -** Changes in taste sensation in human.

| Drugs | Total no. of patients treated | No. of patients reported taste changes (%) |
|---|---|---|
| Metronidazole 500mg x 3 daily | 15 | 11 (73.3) |
| Tinidazole 1 gm daily | 15 | 8 (53.3) |
| Captopril 25mg x 2 daily | 15 | 8 (53.3) |
| Valsartan 80mg daily | 9 | 1 (11.1) |

**Table 4 -** The effect of oral treatment with metronidazole (500mg 3 times daily), tinidazole (1g once daily), captopril (25mg twice daily), and valsartan (80 mg once daily) on serum zinc (µg/dl), and magnesium (mg/dl) in human.

| Treatment | Group I (n=15) Metronidazole | Group II (n=15) Tinidazole | Group III (n=15) Captopril | Group IV (n=9) Valsartan |
|---|---|---|---|---|
| *Before treatment* | | | | |
| Zinc | 89.3±15.1 | 91.3±19 | 89.86±21.24 | 98.7±23.86 |
| Magnesium | 2.45±0.3 | 2.36±0.41 | 2.2±0.32 | 2.22±0.42 |
| *Second weeks after teatment* | | | | |
| Zinc | 85.9±15.2 | 87.2±17.1 | 87±19.6 | 97.6±23.7 |
| Magnesium | 2.4±0.32 | 2.35±0.34 | 2.16±0.32 | 2.17±0.45 |

resulted in a small, but significant reduction in serum zinc level in rabbits following 2 weeks treatment. The effect in human was much smaller and not statistically significant. This might be attributed to a number of confounding factors namely, the difficulty in controlling the type of diet patients might take, in addition to the existence of the disease status. The small reductions of zinc levels in human would specially become important in individuals already at risk of zinc deficiency as children and pregnant women.[17] The proposed mechanism for zinc deficiency is probably chemical interaction with the sulphydryl (SH) group in the chemical structure of metronidazole or tinidazole, an effect that might be responsible for the amoebicidal and antibacterial effect of both drugs. Tinidazole is a structural analogue of metronidazole with similar profile of both clinical uses and adverse effects.[18] Another mechanism is the anorectic effect especially of metronidazole, which resulted in reduction of food intake and body weight of animals. Again, the interaction of anorexia with zinc level require further clarification as anorexia may be the cause of reduced food and nutrient intake and low serum zinc or anorexia occurs secondary to zinc and other nutrient deficiency which cause taste disturbances and reduced food intake. Angiotensin converting enzyme inhibitors as captopril can cause taste disturbances due to zinc deficiency even when there are no changes in serum zinc concentrations.[19] Captopril was shown in laboratory animals to reduce various tissue contents of both zinc and magnesium.[20] However in our study, neither captopril nor any of the other 3 drugs produce any changes in magnesium levels both in rabbits and human. This is probably due to the short duration (2 weeks) of treatment, which may not be enough to alter serum magnesium level. Deficiency of zinc was reported to cause delayed proliferation of taste bud cells.[12] The angiotensin receptor blockers can also blunt taste sensitivity without affecting serum zinc levels.[3] A separate mechanism of taste disturbances by drugs may occur through direct interaction of these drugs with the taste receptors by direct binding and inactivation, interference with the receptors inhibitory proteinse proteins kinase, inositol triphosphate function and ion channels activity ($Ca^{+2}$ and $Na^{+}$).[1] Termination of drug therapy is commonly associated with termination of the taste disturbances. The cells of the taste buds are continuously replaced with each having a life span of 10 days.[21] It was found that the main effect of zinc deficiency were changes in the number and size of taste buds associated with fine structure changes in the taste buds.[22,23] The lack of a significant effect of valsartan on zinc level and taste sensation might point to the role of angiotensin converting enzyme rather than angiotensin

receptors. Metronidazole caused the highest reduction in body weight, while tinidazole, captopril and valsartan reduce the normal increase in body weight during the study period seen in the control group. It is concluded that in rabbit both metronidazole and tinidazole caused lowering of serum zinc levels while tinidazole and captopril (and probably metronidazole) caused degeneration of the taste buds, with no significant effect of valsartan. In human, although the 4 drugs had no effect on zinc levels, they caused taste changes as reported by patients with the least effect caused by valsartan. In this study, we were unable to control the patient's diet, which might affect our results. Studies that control such variables are recommended, as well as the effect of zinc supplementation during treatment with these drugs is required to be investigated in the future.

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