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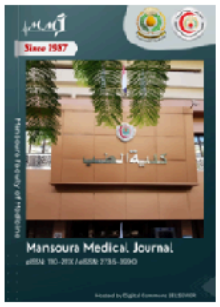

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NATURAL HONEY AS A POTENTIAL DIURETIC (Experimental Study)

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INTRODUCTION

The revelation in the Holy Koran as well as it's decumentation in the hadith clearly described the effectiveness of honey in a variety of diseases (Amir Ali, 1974 and Khan, 1974). Inspite of the attempts that have been made to characterize the pharmacological and scientific aspects of honey, a gap continues to exist between what is known about honey and the hidden miracles of it (Ali, 1989).

In our laboratory while studying the pharmacological effect of honey on blood pressure of dogs an appreciable increase of urine flow was noticed. In addition, earlier reports of other investigators observed that honey could be benefical in treatment of some renal diseases and they suggested that honey could be benefical in treatment of som renal diseases and they suggested that honey through it's effect on adjustment of osmosis could produce diuresis especially in cases of heart failure, renal failure and oedema (Shoker, 1985). These observations stimulated us to explore the potential diuretic effect of honey in a well controlled experimental study in dogs.

MATERIAL AND METHODS

Fifteen mongrel dogs of either sex, 6 to 10 kgm each were housed under similar conditions and fed similar diet at least for 2 weeks before the experiments. Assay of the diuretic activity was performed according to the method described by Lohmoller et al.,

(1975) and Cohen et al., (1976): After an overnight fasting each dog was anaesthetized with sodium pentobarbital (30 mg/kgm I.V.) and artificially ventilated by a Harvard respirator. The right femoral vein was cannulated for fluid and drug administration. Intravenous saline infusion 20 ml/kgm body weight was given as a hydrating dose, followed by 0.33 milliliter saline/ kgm body weight/ minute throughout the experiment. The urinary bladder of the animal was exposed by a midline incision over the lower part of the abdomen. Both ureters were identified, cleared and cannulated about an inch above the urinary bladder with polyethylene tubing. Urine collections from both kidneys were pooled and volumes were measured in graduated cylinders every 20 minutes. Control observations were recorded for one hour. The test compound was then injected intravenously and urine was collected and volume recorded every 20 minutes for a further period of one hour. Blood samples were obtained at the midpoint of each urine collection period. Each urine or serum sample was analyzed for sodium and potassium by flame photometer (Willard et al.,1965) and for chloride concentration (Schales, 1953).

The results obtained in the periods following compound treatment were compared with those of the corresponding control periods before compound administration. The diuretic activity was calculated acoording to the following equation : (Logmann & Giraldi, 1958) .

Activity = urinary excretion after treatment / urinary excretion before treatment

The dogs were divided into three groups each of 5 animals. One group was used to demonstrate the response to a standard diuretic drug namely hydrochlorothiazide 2.5 mg/ kgm, I.V. (Sweat&GauL,1975). The second group received honey intravenously 1gm/kgm in a 40% dil. in normal saline (Deller,1971 and Bizzi,1985). The third group received a glucose fructose - maltose (GFSM) mixture in a dose equal to the dose of honey used in the second group and at the same dilution. This mixture was prepared by mixing these sugars together in the same proportions as they are found in natural honey viz: glucose 31 gm/100 ml., fructose 38 gm/100 ml, sucrose

1.3 gm/100 ml and maltose 7.3 gm/ 100 ml (Al i, 19 89).

RESULTS

Hydrochlorothiazide 2.5 mg/kgm I.V. significantly augmented the volume of urinary output, urinary sodium, chloride and to a less extend potassium excretion. The diuretic effect started immediately after hydrochlorothiazide injection and reached maximum in the 2nd collection period and started to decline in the 3rd collection period of the drug phase (Table I) .

Table II demonstrates that I.V. honey (1gm/kgm) produced prompt and significant increase in urlne volume, sodium, potassium and chlorlde excretion. These effects also reached maximum values in the 2nd collection period and started to decrease by third collection period although there was still significant diuretic effects as compared to the corresponding control period. The diuretic and saluretic activity of honey is more or less equal to that of hydrochlorothiazide, but honey had less kaluretic effect (Table IV).

I.V. injection of GFSM mixture (1 gm/kgm) produced no significant changes of urine flow, sodium, potassium or chloride excretion (Table III). Serum sodium, potassium and chloride concentrations were maintained unaltered in all groups, except for slight hypokalaemia in the group treated with hydrochlorothiazide (Table V).

DISCUSSION

Hydrochlorothiazide was selected as a standard diuretic drug because it has a moderate potency and an average duration of action, these make comparative study more expressive. The diuretic effect of I.V. hydrochlorothiazide in dogs had been demonstrated early by Baer et al., (1959) and Beyer & Baer, (1959) . It was stated that diuresis started immediately after I.V. injection of chlorothiazide or hydrochlorothiazide and reached maximum within 30 minutes. hydrochlorothiazide significantly inerease urine volume, sodium, chloride and to a less extent potassium. Chloride ion appears to be the main attending anion accompanying cation excretion (Beyer, 1958 and Lohmoller et al., 1975). This pattern of diuretic effect of hydrochlorothiazide as well as the magnitude of this effect, compare vourably with the response obtained in

the present study. The only significant change in serum electrolytes following I.V. hydrochlorothiazide injection is slight hypokalaemia, this is also in agreement with Lohmoller et al., (1975).

Honey 1 gm/kgm I.V. produced a statistically significant augmetation in urine output and urinary excretion of sodium, chloride and to a less extent of potassium. The pattern of response is largely comparable to that of hydrochlorothiazide, it started immediately, reached a maximum in the 2nd 20 minutes collection period. Furthermore, the potency of diuretic activity is more or less equal to that of hydrochlorothiazide with similar marked natriuresis covered with comonsurate increase of chloride ion excretion but kaluresis. The finding that honey produced less kaliuresis than hydrochlorothiazide could largely explain why honey did not produce significant hypokalaemia like hydrochlorothiazide. The intravenous injection had been documented to be a safe route for administration of honey Deller (1971) used I.V. injection of honey for few days in treatment of eczema, also, Bizzi (1985) used honey I.V. in a 40 % dilution during labour to get less painful delivery.

The present study is by far the first report on the diuretic effect of honey. It may be argued that the possible mechanism of diuretic effect of honey is through an osmotic action of it's hypertonic sugar content. However, this assumption seems incorrect because a mixture prepared of glucose - fructose - sucrose - maltose (GFSM) in the same proportions as they are found in natural honey failed to produce any diuretic effect in the present study. The possibility that honey could act as acidifying diuretic could be suggested, since honey is known to be acidic in nature PH 3.6 (White, 1975). However, the magnitude of the diuretic activity of honey is much higher than could be expected from an acidifying agent. Thorefore, the mechanism of action of honey could not be solely through this mechanism. Honey was found to inhibit pepsin enzyme activity in the stomach, possibly through it's colloidal nature that cause adsorption of the enzyme and/or due to its sugar acid oontent as gluconic acid (Baillie&Anderson, 1968 and Hegazy et nl.,1981). Accordingly, it could

be assumed that honey may interfere with renal tubular enzyme activity and affect tubular transport of ions.

Moreover, renal prostaglanains (PGE2 and PGF2) were reported to have natriuretic effect in man (Lee et al., 1971 a & b) and animals (Fulgraff et al., 1974 and Fine & Trizha, 1977) when administered intra-arterially or intravenously. Consequently, theories have appeared which designated an important role of prostaglandins as mediators of natriuresis (Dunn & Hood, 1977). Since honey was documented to counteract indomethacin induced inhibition of prostaglandins synthesis (Ali et al., 1990), it is likely that the diuretic effect of honey could be, at least in part may be, mediated through an action on renal prostaglandins.

Finally, the hidden merits of honey which are not yet uncovered to human can't be ignored (Ali, 1989). The diuretic effect of honey may be due to some of these hidden miracles

Although the various mechanisms of action and site of action at renal tubules have not been elucidated, this is the frist study which provides a controlled scientific evidence for the diuretic activity of honey. However, it is worthy to suggest, that further studies of the diuretic effects of honey at different doses and for different durations and by various routs of administration and it's diuretic effect in conditions of acidosis or alkalosis as well in oedematous animals. Also, determination of the site of action by different techniques are required to complete the study of the diuretic effect of this effective and notably safe potential diuretic and to ascertain its clinical potential. In addition, assessment of the effects of honey on the renal tubular enzyme activity, renal haemodynamics and renal prostaglandins are also needed in order to explore the possible underlying mechanism (s) of the diuretic effect of honey.

SUMMARY

In this study the potential diuretic effect of honey was investigated in anaesthatized dogs and oompared to hydrochlorothiazide as a standard diuretic drug.

Intravenous administration of honey 1 gm/kgm in a 40 % dilution in normal saline produced significant augmentation of volume of urine output, urine sodium, chlorlde and to less extent potassium excretion. The increase in cation excretion is covered with commonsurate increase of chloride ion i.e. chloride ions appears to be the main attending anion. The diuretic effect of honey starts immediately after administration and reachs maximum after 20 to 40 minutes. The pattern of diuretic effect of honey as well as the magnitude of this effect, compare favourably with the response to hydrochlorothiazide (2.5 mg/kgm I.V), However, honey has the advantage that it produces less kaliuresis. Measurement of serum concentration of sodium, chloride and potassium following administratlon of honey or hydrochlorothiazide revealed that concentrations of these ions are not altered except the potassium concentration which shows mild hypokalaemia in dogs treated with hydrochlorothiazide.

A mixture of glucose-fructose - sucrose - maltose (GFSM) in the same proportions as they are found in honey was tested in a group of dogs in a dose of 1gm/kgm i.e. equal to the dose of natural honey, this mixture failed to produce any diuretic effect. Such finding could suggest that the diuretic effect of honey is not attributed to its sugar content. Although the various mechanisms of action or the site of the diuretic effect at the nephron have not been elucidated, this is the first study which provides a controlled scientific evidence for the potential diuretic effect of honey. These preliminiry results suggest that honey may be used clinically as a safe diuretic. However, further investigations are required to explore the mechanism (s) of this property and fully to ascertain it's clinical potential.

Table I : Effect of hydrochlorothiazide on urine output and electrolytes excretion by anaesthetized dogs .

TREATMENT	Time (min .)	Urine Output (ml . / mon .)	Electrolyte Excretion (uEq / min .)		
			Sodium	Potassium	Chloride
Control Phase . (Saline 2me / Kgm. I . v .)	- 60 to - 40 - 40 to - 20 - 20 to 0	1.3 ± 0.05 1.1 ± 0.06 1.5 ± 0.08	43 ± 3.12 50 ± 3.91 45 ± 3.20	48 ± 3.61 50 ± 4.12 42 ± 4.22	0 ± 4.82 58 ± 4.13 66 ± 5.11
Hydrochlorothiazide Phase . (2.5 mg / kg . I . V .)	0 to 20 20 to 40 40 to 60	6.4 ± 0.21 * 7.2 ± 0.22 ** 5.2 ± 0.31 **	240 ± 11.10 * 288 ± 13.21 ** 200 ± 13.02 **	100 ± 4.70 * 118 ± 5.61 ** 91 ± 5.21 **	270 ± 10.21 * 310 ± 12.11 ** 235 ± 9.01 **

- All values represents the mean of 20 min collection period for a group of 5 dogs . ± Standard Error .

* Significant difference between the means of the 20 min . collection periods of hydrochlorothiazide phase and the corresponding periods of the control phase ($p < 0.05$) .

* Siginificant difference between the 1st and the other two collection periods of hydrochlorothiazide phase ($p < 0.05$).

Table II : Effect of natural honey on urine output and electrolyte excretion by anaesthetized dogs .

TREATMENT	Time (min .)	Urine Output (ml . / m.n .)	Electrolyte Excretion (uEq / min .)		
			Sodium	Potassium	Chloride
Control Phase. (Saline 2ml / Kgm. I . v .)	- 60 to - 40 - 40 to - 20 - 20 to 0	0.9 ± 0.03 1.0 ± 0.06 1.1 ± 0.08	47 ± 3.21 42 ± 2.72 37 ± 1.81	48 ± 2.81 39 ± 2.11 46 ± 3.01	50 ± 4.13 51 ± 3.91 49 ± 3.82
Honey Phase . (1 gm / kgm . I . V .)	0 to 20 20 to 40 40 to 60	4.0 ± 0.22 * 5.2 ± 0.23 ** 3.4 ± 0.11 **	235 ± 11.23 * 295 ± 22.11 ** 200 ± 10.21 **	80 ± 4.21 * 97 ± 6.01 ** 64 ± 4.02 **	220 ± 10.21 * 270 ± 11.01 ** 187 ± 8.22 **

- All values represents the mean of each 20 min collection period for a group of 5 dogs . ± Standard Error .

* Significant difference between the means of the 20 min - collection periods of honey phase and the corresponding periods of control phase ($p < 0.05$) .

* Siginificant difference between the 1st and the other two collection periods of honey phase.

Table III : Effect of GFSM* mixture on urine output and electrolytes excretion by anaesthetized dogs .

TREATMENT	Time (min .)	Urine Output (ml . / min .)	Electrolyte Excretion (uEq / min .)		
			Sodium	Potassium	Chloride
Control Phase . (Saline 2 ml / Kgm. I . v .)	- 60 to - 40	0.8 ± 0.03	37 ± 2.11	31 ± 2.51	50 ± 4.11
	- 40 to - 20	1.1 ± 0.04	40 ± 3.23	33 ± 2.62	40 ± 3.01
	- 20 to 0	0.9 ± 0.05	41 ± 2.91	40 ± 2.41	39 ± 2.09
GFSM * mixture (1 gm / kgm . I . V .)	0 to 20	1.2 ±0.04@	40 ± 2.12@	38 ± 2.31@	45 ± 3.09@
	20 to 40	0.8 ± 0.03@	39 ± 2.34@	39 ± 2.52@	40 ± 2.91@
	40 to 60	0.8 ±0.04@	42 ± 3.10@	34 ± 2.60@	44 ± 3.03@

- All values represents the mean of each 20 minute collection period ± Standard Error .

* GFSM : a mixture of glucose , furactose, sucrose and maltose in the same proportions present in natural honey .

@ Non siginficant difference between the means of GFSM mixture phase collection periods and the corrasponding control phase periods (p>0.05) .

Table IV : Comparison of the diuretic activity of hydrochlorothiazide and honey in anaesthetized dogs .

TREATMENT	Urine Output (ml . / min .)	Electrolyte Excretion (uEq / min .)		
		Sodium	Potassium	Chloride
Control Phase (Saline 2ml / Kgm. I. v.)	1.3 ± 0.09 *	47 ± 1.69 *	47.67 ± 1.19 *	61.3 ± 1.96 *
Hydrochlorothiazide phase (2.5 mg / kgm . I . v .)	6.27 ± 0.47	242.7 ± 20.8	103 ± 6.48	271.7 ± 14.14
Activity °	4.82 ± 0.25	5.16 ± 0.39	2.16 ± 0.12	4.43 ± 0.38
Control phase (saline 2ml / kgm)	1 ± 0.05 *	42 ± 2.36 *	44.33 ± 2.23 *	50 ± 0.47 *
Honey Phase (1 gm / kgm . I v .)	4.27 ± 0.39	246.67 ± 20.59	80.33 ± 7.78	225.67 ± 19.05
Activity °	4.27 ± 0.31	5.87 ± 0.41	1.61 ± 0.08*	4.51 ± 0.36

- Each value represents the mean of triplicate successive 20 minutes collection periods for a group of 5 dogs ± Standard Error .

* Significant difference from the corresponding control phase ($p<0.05$)

o Activity = $\frac{\text{Urinary excretion of treatment phase}}{\text{Urinary excretion of control phase .}}$

* Significance from hydrochlorothiazid activity ($p < 0.05$) .

Table V : Effect of hydrochlorothiazide and honey on serum electrolytes concentrations.

	Hydrochlorothiazide 2.5mg / kgm . I . V . (n = 5)			Honey 1 gm / kgm . I . V . (n = 5)		
	Before	After	P	Before	After	P
Serum Sodium (mean mEq / L ± S . E .)	145.2 ± 10.23	143.7 ± 9.96	N.S.	149 ± 11.21	147.9 ± 9.91	N.S.
Serum Potassium (mean mEq / L ± S . E .)	3.99 ± 0.24	3.21 ± 0.19	<0.05	4 ± 0.31	3.93 ± 0.23	N.S.
Serum Chloride (mean mEq / L ± S . E .) .	110.8 ± 7.41	110.8 ± 5.95	N.S.	107.2 ± 8.11	106.9 ± 8.21	N.S.

S . E . = Standard Error .

P = Significance of the difference between the mean values after and before treatment .

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دراسة تجريبية لعسل النحل الطبيعى كمدر للبول

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د / محمد عهدى عطيه على سعد د / كريمة السبخاوى
من اقسام الفارماكولوجى والكيمياء الحيوية بكلية الطب - جامعة المنصورة

تم فى هذا البحث دراسة مدى فاعلية عسل النحل الطبيعى كمدر للبول فى الكلاب المخدره ومقارنة مفعوله بتأثير احد مدرات البول المعروفه (الهيدروكلوروثيازيد) .

وقد وجد ان اعطاء عسل النحل (جم لكل كليو جرام من وزن الجسم عن طريق الحقن الوريدى بعد تخفيض نسبة ٤٠٪ فى محلول ملح طبيعى يحدث زيادة ذات دلاله احصائيه هامه فى حجم البول وفى اخراج الصوديوم والبوتاسيوم والكلوريد . وقد لوحظ أن الزياده فى اخراج الصوديوم والبوتاسيوم مصحوبه بزياده معادلة فى اخراج الكلوريد مما يشير الى ان الكلوريد هى الانيون الرئيسى الذى يزيد اخراجه كما لوحظ ان هذه الزياده فى اخراج البول تبدأ مباشرة بعد حقن العسل وتبلغ اقصى درجاتها خلال الفترة من ٢٠ الى ٤٠ دقيقة بعد حقن العسل .

وبمقارنة تأثير عسل النحل بالهيدروكلوروثيازيد وجد أن طبيعية ومقدار ادرار البول الناتج عن حقن العسل تماثل الى حد كبير التأثير الناتج عن حقن الهيدروكلوروثيازيد فى الوريد ٢,٥ مجم لكل كيلو جرام من وزن الجسم ولكن العسل يمتاز عن الهيدروكلوروثيازيد بأنه يحدث زياده اقل فى اخراج البوتاسيوم كما انه لايحدث نقص فى عنصر البوتاسيوم فى مصل الدم كذلك الذى يظهر عند حقن الهيدروكلوروثيازيد .

وقد وجد أيضا ان محلول الخليط من سكر العنب ، سكر الفواكه ، سكر القصب ، سكر الشعير بنفس النسب التى توجد بها هذه السكريات فى عسل النحل الطبيعى عند حقنه بالوريد بنفس الجرعة والتخفيف المستخدمين فى اعطاء العسل لم يحدث اى تأثير له دلاله احصائيه فى معدل اخراج البول . الامر الذى يوضح أن تأثير العسل المدر للبول لايمكن ان يكون ناتج عن محتوياته من هذه السكريات .

وعلى الرغم ان هذا البحث لم يستكمل دراسة ميكانيكية عمل عسل النحل كمدر للبول الا انه يعتبر الدراسة الاولى التى تعطى دليلا علميا تجريبيا عن فاعلية عسل النحل كمدر للبول . وان كانت نتائج هذا البحث تشجع فكرة استخدام عسل النحل اكلينيكيا كمدر طبيعى للبول له درجة كبيرة من الامان بعيد عن الاثار الجانبية للادويه الاخرى الا ان الحاجه مازالت مستمره لمزيد من الدراسه لآلية عمل عسل النحل وللتأكد من مدى فاعليته فى الانسان .