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<p>(21) International Application Number: PCT/CA99/00331</p> <p>(22) International Filing Date: 16 April 1999 (16.04.99)</p> <p>(30) Priority Data: 09/061,173 16 April 1998 (16.04.98) US</p> <p>(71) Applicants: UNIVERSITY OF MANITOBA [CA/CA]; 202 Administration Building, 56 Chancellors Circle, Winnipeg, Manitoba R3T 2N2 (CA). MEDICURE INC. [CA/CA]; 24-62 Scurfield Boulevard, Winnipeg, Manitoba R3Y 1M5 (CA).</p> <p>(72) Inventors: DAKASHINAMURTI, Krishnamurti; 9934 Crest View Park Drive, Winnipeg, Manitoba R2Y 0V7 (CA). SETHI, Rajat; 68 Sauve Crescent, Winnipeg, Manitoba R2N 3K9 (CA). DHALLA, Naranjan, S.; 52 Riverpoint, Winnipeg, Manitoba R2M 5N6 (CA).</p> <p>(74) Agent: HIRONS, Robert, G.; Ridout & Maybee, 18th floor, 150 Metcalfe Street, Ottawa, Ontario K2P 1P1 (CA).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <div style="border: 1px solid black; padding: 10px; margin: 10px auto; width: fit-content;"> <p style="text-align: center;">IP AUSTRALIA</p> <p style="text-align: center;">8 NOV 1999</p> <p style="text-align: center;">RECEIVED</p> </div>	
<p>(54) Title: TREATMENT OF IATROGENIC AND AGE-RELATED HYPERTENSION AND PHARMACEUTICAL COMPOSITIONS USEFUL THEREIN</p>		
<p>(57) Abstract</p> <p>Hypertension in mammalian patients, especially elderly human patients, derived from ingestion of NSAIDs or through the normal aging process is treated by administration to the patient of a vitamin B₆ (or derivative) supplement. Where the patient requires the continued administration of an NSAID for pharmacological purposes, the NSAID is administered in conjunction with a vitamin B₆ supplement. The invention further provides combination pharmaceutical combinations of an NSAID and a vitamin B₆ supplement, e.g. orally administrable tablets or capsules, for use in treating such conditions.</p>		

TREATMENT OF IATROGENIC AND AGE-RELATED HYPERTENSION AND
PHARMACEUTICAL COMPOSITIONS USEFUL THEREIN

FIELD OF THE INVENTION

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This invention relates to pharmaceutical compositions and combinations, and uses thereof in medical treatment. More specifically, it relates to treatment of hypertension and to pharmaceutical compositions and combinations useful therein, especially treatment of hypertension in human
10 patients on NSAID treatment.

BACKGROUND OF THE INVENTION

The occurrence of hypertension (elevated blood pressure) in the
15 elderly is high. This is also the age group with a high incidence of arthritis. Osteo-
arthritis is common after the age of 40. The presence of an inflammatory
component to osteo-arthritis is now recognized. About 30% of patients with
arthritis also have hypertension. Thus there is a considerable potential for the
concurrent prescription of non-steroidal anti-inflammatory drugs (NSAIDs) and anti-
20 hypertensives in the elderly population group. It is estimated that, in the United
States, more than 20 million people are on concurrent anti-hypertensive and
NSAID therapy. It is known that most anti-hypertensive agents are less effective
in the presence of NSAIDs.

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In the past several years, there have been various reports of adverse
effects of NSAIDs in patients receiving any form of anti-hypertensive medication
such as β -blockers, angiotensin converting enzyme inhibitors and diuretics. The
hypotensive (blood pressure lowering) effect of β -blockers is attenuated by the
combined administration of NSAIDs such as indomethacin, sulindac and piroxicam.
30 Significant attenuation of the hypotensive effect of the angiotensin-converting
enzyme inhibitor captopril by indomethacin, acetylsalicylate and

sulindac has been reported. The antagonism by NSAIDs of the hypotensive effects of diuretics such as furosemide and hydrochlorothiazide has also been reported. Naproxen and piroxicam have been reported to raise blood pressure of patients significantly during the concomitant use of drugs such as β -blockers and diuretics. Most NSAIDs appear to reduce the anti-hypertensive effect of a variety of anti-hypertensive drugs, with the exception of the calcium channel blockers, which in any event have recently been reported to have other adverse side effects. Patients with renal impairment are at a risk of developing renal side effects when NSAIDs are used. In the elderly population suffering from various arthritic disorders, the potential adverse interaction between anti-inflammatory and anti-hypertensive drugs poses a significant problem. Treatments that maintain the anti-hypertensive action would be very beneficial to this age group.

BRIEF REFERENCE OF THE PRIOR ART

Paulose, C.S., Dakshinamurti, K., Packer, S.C. and Stephens, N.L., "Sympathetic Stimulation and Hypertension in the Pyridoxine-deficient Rat", Hypertension, Vol. 11, pages 387-391, 1988, reports work that shows that a moderate deficiency of vitamin B₆ in rats causes hypertension which is reversed within 24 hours by the administration of vitamin B₆ in the form of pyridoxine.

U.S. Patent 4,374,841 reports that pyridine derivatives such as 4,5-dihydroxymethyl-3-[2-hydroxy-3-(2-methylphenoxyethylamino)-propoxy]-2-methylpyridine and 4,5-dihydroxyethyl-3-[2-hydroxy-3-(2-methoxyphenoxyethylamino)-propoxy]-2-methyl-pyridine reduce the epinephrine-increased blood pressure in dogs.

U.S. Patent 4,564,614 reports the use of pyridoxine or its salts in an improved anti-inflammatory composition to reduce gastric irritation on administration of NSAIDs.

5 Baker, Eric J., Reed, Kurt E., and Dixon, Steven L. "Chlorthalidone-induced pseudoporphyria: Clinical and Microscopic Findings of a Case", Journal of the American Academy of Dermatology, Vol. 21, page 1026-1029 reports the case of a patient presenting with pseudoporphyria who, at the time of presentation, was receiving pyridoxine and aspirin.

10 Jacobs, Laurie G. "The Neuroleptic Malignant Syndrome: Often an Unrecognized Geriatric Problem", Journal of the American Geriatric's Society, Vol. 44; No. 4, pages 474-5, 1996, reports a women who presented with apparent Neuroleptic Malignant Syndrome, and at the time of presentation, had
15 hypertension and was receiving medications including aspirin and pyridoxine.

Some nutritional studies, namely Vanderjagt, D.J. and Garry P.J., "Vitamin B₆ Status in a Healthy Elderly Population", Ann. N. Y. Acad. Sci., Vol. 585, page 562-564, 1990, and Kok, F.J. et al., "Low Vitamin B₆ Status in Patients with Acute Myocardial Infarction", Am. J. Cardiol., Vol. 63. pages 513-516, 1989, indicate that the elderly may be at increased risk for developing a deficiency of vitamin B₆.

The present invention provides novel pharmaceutical combinations which are useful in treating hypertension in patients.

The present invention further provides combinations of NSAIDs with other pharmaceutical, which can be used for treating hypertension without serious loss of the anti-inflammatory activity of the NSAID.

The present invention further provides novel treatments of hypertension in patients suffering therefrom and under NSAID treatment, especially in adult human patients.

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SUMMARY OF THE INVENTION

The present invention is based upon the discovery that vitamin B₆ and derivatives thereof attenuate the hypertension induced by anti-inflammatory drugs such as the NSAIDs. Blood pressure in hypertensive mammals is significantly and rapidly reduced by administration to the patient of vitamin B₆ or derivative supplement. Meta analysis of various studies indicates that the ingestion of NSAIDs attenuates the anti-hypertensive effect of a variety of anti-hypertensive drugs such as β -blockers, angiotensin-converting enzyme inhibitors and diuretics, which reduces or even negates the usefulness of such drugs as anti-hypertensives when NSAIDs are also used.

Thus the present invention provides use of vitamin B₆ or a derivative thereof in the preparation of a medicament for use in the treatment of hypertension in a patient having hypertension and under treatment by one or

more NSAIDs.

The present invention further provides a method of alleviating hypertension in a mammalian patient who has hypertension under treatment by NSAIDs, which comprises
5 administering to the patient an effective amount of a vitamin B₆ supplement or vitamin B₆ derivative supplement.

The invention further provides use in preparation of a medicament for treating hypertension in a mammalian patient caused by treatment of the patient with
10 one or more NSAIDs, of a vitamin B₆ (or derivative) supplement selected from pyridoxine, pyridoxine hydrochloride, pyridoxal, pyridoxal-5-phosphate, pyridoxamine and 4-pyridoxic acid.

The invention further provides use in preparation of a medicament for treating hypertension in a
15 mammalian patient, of both an NSAID and a vitamin B₆ (or derivative) supplement selected from pyridoxine, pyridoxine hydrochloride, pyridoxal, pyridoxal-5-phosphate, pyridoxamine and 4-pyridoxic acid.

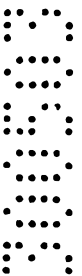
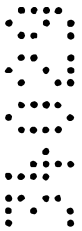
According to another aspect, the present invention provides a process of treating a mammalian patient in need of the beneficial effects of a non-steroidal anti-inflammatory drug (NSAID) without causing
20 excessive hypertension in the patient, which comprises administering to the patient an effective amount of an NSAID in conjunction with a vitamin B₆ supplement or vitamin B₆ derivative supplement.

According to a further aspect, the invention provides pharmaceutical compositions for treating NSAID-
30 induced hypertension in aged mammalian patients, comprising an effective amount of a vitamin B₆ supplement or vitamin B₆ derivative supplement.

For the purposes of this specification it will be clearly understood that the word "comprising" means
35 "including but not limited to", and that the word "comprises" has a corresponding meaning.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Since elderly human patients commonly suffer from osteo and rheumatoid arthritis or similar conditions for
5 which NSAIDs are the recommended treatment, and since elderly patients commonly suffer from hypertension, the present invention is particularly suitable for use with elderly human patients, and this is its preferred application. Thus it is of particular significance under
10 conditions (i) where the patient is ingesting anti-inflammatory drugs, including over-the-counter anti-inflammatory drugs, e.g. for treatment of osteo or rheumatoid



arthritis, and (ii) in age-related hypertension in the elderly. However, the invention is not so limited and provides beneficial effects for substantially all mammalian patients suffering from hypertension.

The range of NSAIDs which can be beneficially included in the compositions and treatments according to the present invention is very wide, and extends to substantially all of the known NSAIDs currently available on the market. Specific NSAIDs which may be used in the present invention include diclofenac, indomethacin, the various anti-inflammatory acetylsalicylates (e.g. aspirin), sulindac, alclofenac, amfenac, piroxicam, naproxen, fenoprofen, ibuprofen, ketoprofen, flurbiprofen, alminoprofen, ketorolac, GOBAB (3-amino-4-hydroxybutyric acid), amixetrine, diflunisal, mefenamic acid, phenylbutazone, tiaprofenic acid and tolmetin. Specifically preferred are diclofenac, indomethacin and the acetylsalicylates.

The vitamin B₆ derivatives contemplated for use in the present invention are those which are chemical modifications of vitamin B₆, sometimes formed in the body as metabolites thereof, and having the same ring nucleus, for example pyridoxal-5-phosphate, pyridoxal, pyridoxamine, 4-pyridoxic acid, etc.

The vitamin B₆ supplement used in the present invention is preferably pyridoxine in any of its pharmaceutically acceptable forms, such as pyridoxine hydrochloride addition salt. The amount of vitamin B₆ compound or supplement used in the present invention is preferably from about 10 mg to about 500 mg, most preferably from about 50 to about 100 mg, per 70 kg of body weight of the patient, of vitamin B₆ pyridoxine hydrochloride, or related compound acting as a vitamin B₆ (or derivative) supplement, for administration on a daily or twice daily basis,

to an adult human patient.

The amount of NSAID administered to the patient, in the process of the invention, does not normally change from the prescribed dosage being used to treat the inflammatory condition in the absence of the vitamin B₆ (or derivative) supplement. Thus, a patient taking a daily dosage of, say, 500 mg of naproxen to treat or alleviate an underlying inflammatory condition continues to take the same prescribed 500 mg thereof supplemented by vitamin B₆ or derivative in the process of the invention. Suitable prescribed doses vary widely according to the choice of NSAID, the underlying conditions it is intended to alleviate, and factors concerning the individual patient. Generally appropriate dosage ranges may be found by consulting standard reference pharmacopeias, and thus are well within the skill of the art. As examples, indomethacin is commonly prescribed for rheumatoid arthritis at an oral dosage rate of 75-200 mg per day, in three separate doses per day. Diclofenac is commonly prescribed for rheumatoid arthritis and osteoarthritis, at a daily oral dosage rate of 75-150mg, in three separate doses per day. Acetylsalicylates are generally administered in higher dosages, such as 650 mg, four to six times per day as necessary to alleviate the symptoms. The same NSAID dosage rates as prescribed, are continued in the process and formulations of the invention.

A specific preferred embodiment of the present invention is a dosage form pharmaceutical composition for administration to patients requiring NSAID therapy, comprising in combination an effective amount of an NSAID and an amount of vitamin B₆ (or derivative) supplement effective to alleviate the hypertensive effects of the NSAID. Such a formulation suitably takes the form of an orally administrable tablet or capsule, with

appropriate inert, tablet forming ingredients. The amount of NSAID in such a tablet or capsule may be in the range of 25-1000 mg, depending on choice of NSAID, condition to be treated, frequency of administration, etc. The amount of vitamin B₆ (or derivative) supplement in such a tablet or capsule may be in the range 10-500 mg. Such a combined drug formulation provides effective therapy upon administration.

Whilst it is most convenient and preferred to prepare and use compositions which comprise a combination of the NSAID and the vitamin B₆ or derivative, e.g. in a tablet or capsule form, along with suitable pharmaceutical carriers, diluents, excipients and the like, for oral administration, other methods of administration are within the scope of the present invention. For example, the active ingredients, namely the NSAID and vitamin B₆ or derivative, may be administered separately and sequentially to the patient, and the combined or sequential administration may be via the oral route, or alternatively parenterally, intramuscularly, rectally, transcutaneously or nasally. Formulations of the compositions of the present invention for such forms of administration are standard and within the skill of the pharmaceutical compounders art.

Vitamin B₆ is a known but not commonly prescribed anti-hypertensive agent, although not previously known to be effective in the presence of NSAIDs. A substantial advantage of its use is that it is known to be non-toxic and to lack side effects in the proposed human dosage of up to 600 mg/person/day, having previously been so used, for example, in long term treatment of chronic anemia.

SPECIFIC EXAMPLES

The following specific examples further describe and illustrate the present invention and its use, but are not to be construed as limiting on the scope of the invention. They describe the invention in relation to its use on laboratory animals, in accordance with approved practices. Laboratory rats, some having a moderate hypertension condition and some being normal, normotensive rats were used, taking measurements of their systolic blood pressure in acute and long term experiments using compositions according to the invention. The hypertensive rats were on a vitamin B₆ deficient diet for 8-10 weeks prior to the experiments. They had a body weight of 200-225 g. The control normotensive rats weighed about 300 g.

EXAMPLE 1 - (Control)

The time and dosage response of hypertensive rats to treatment with diclofenac was investigated.

Vitamin B₆ deficiency-induced hypertensive rats (prepared according to the procedures of Paulose et al., cited above) were used in acute experiments. They were injected with varying doses of diclofenac and the changes in systolic blood pressure (SBP) were monitored by tail cuff plethysmography. In vitamin B₆-deficient hypertensive rats (SBP, 150 mm Hg), intraperitoneal injection of diclofenac sodium (dose, 1 mg/kg body weight) raised the SBP by 9 mm Hg in one hour after injection. A higher dose (3 mg/kg) elevated SBP by 28 mm Hg, which also occurred one hour after injection. A larger dose (10 mg/kg) caused an increase of SBP of similar magnitude but the effect lasted for 2 hours.

EXAMPLE 2 - (Control)

The effects of treatment with indomethacin on the SBP of hypertensive rats was investigated.

The effect of varying doses (1 or 3 mg/kg body weight) of indomethacin on the SBP of hypertensive rats was examined by monitoring SBP tail cuff plethysmography following intraperitoneal injection of the drug or vehicle to the rats. Indomethacin (3 mg/kg) raised the blood pressure of hypertensive rats by 6 mm Hg within thirty minutes. The peak response (35 mm Hg) was reached by one hour. Although the effect declined by two hours, it was still elevated (15 mm Hg) and vehicle injected levels were reached only after three hours. A smaller dose (1 mg/kg) did not have any effect on the SBP of the hypertensive rat.

In the following Examples 3, 4 and 5, the effects of oral administration of various NSAIDs up to seven days on the SBP of rats on a normal diet were examined. Older (chronological age) normal rats (400-600 g body weight) on a commercial rat diet (chow) were used. These rats had a SBP of 145-150 mm Hg.

EXAMPLE 3

The effect of oral administration of a vitamin B₆ supplement (2.5 or 5 times the daily requirement) on SBP of older rats was examined. The rats were divided into four groups. Group 1 was continued on the same commercial rat chow ration. Group 2 was fed the same diet containing diclofenac (100 mg per kg diet). Group 3 was fed the commercial rat chow diet containing a vitamin B₆ supplement (2.5 or 5 times the daily requirement for vitamin B₆, i.e. 25 mg/kg and 50 mg/kg

respectively). Group 4 was fed diclofenac as in Group 2 but also had the vitamin B₆ supplement in the same amounts. The animals consume about 15 grams of chow per day. The SBPs were determined on days 0 (6 hours after start of feeding), 1 and 7, at the same time (late afternoon) for each measurement. The results are given in Tables 1(a) for 2.5 times vitamin B₆ supplement and in Table 1(b) for 5 times vitamin B₆ supplement. In the Tables, each value is the mean \pm S.E.M. of 5 rats. Body weight is indicated by B.Wt., systolic blood pressure by SPB and heart rate by HR.

Table 1(a)

Group	0 Day on Diet			1 Day on Diet			7 Days of Diet		
	B.Wt. (g)	SBP (mm Hg)	HR (beat/min)	B.Wt. (g)	SBP (mm Hg)	HR (beat/min)	B.Wt. (g)	SBP (mm Hg)	HR (beat/min)
1	413 \pm 6	145 \pm 1	345 \pm 5	-	148 \pm 2	350	418 \pm 18	146 \pm 1	345 \pm 5
2	414 \pm 15	145 \pm 2	335 \pm 10	-	148 \pm 1	345 \pm 5	418 \pm 20	147 \pm 1	330 \pm 5
3	431 \pm 7	146 \pm 1	350 \pm 9	-	135* \pm 1	345 \pm 5	446 \pm 9	136* \pm 1	325 \pm 11
4	415 \pm 6	145 \pm 2	345 \pm 5	-	123* \pm 2	335 \pm 13	416 \pm 11	120* \pm 2	325 \pm 8

*P< 0.05 with respect to normal chow or normal chow plus Diclofenac (100 mg/kg diet)

TABLE 1(b)

Group	0 Day on Diet			1 Day on Diet		
	B.Wt. (g)	SBP (mm Hg)	HR (beat/min)	B.Wt. (g)	SBP (mm Hg)	HR (beat/min)
1	565 \pm 15	148 \pm 1	345 \pm 10	-	147 \pm 1	350 \pm 10
2	560 \pm 13	148 \pm 1	350 \pm 12	-	149 \pm 1	350 \pm 10
3	563 \pm 16	148 \pm 1	350 \pm 8	-	124* \pm 1	350 \pm 10
4	561 \pm 12	149 \pm 1	330 \pm 8	-	108* \pm 1	335 \pm 8

*P<0.05 with respect to normal chow or normal chow plus Diclofenac (100 mg/kg diet)

These results indicate that, even on day 1, vitamin B₆ supplementation alone gives a significant decrease in SBP (Group 3 results in comparison with Group 1 results). Diclofenac alone had little effect (Group 2 results), but the combination of vitamin B₆ supplement and diclofenac (Group 4) was most marked. Vitamin B₆ supplement decreased the SBP of older rats. The effect was quite significant even when the rats were receiving diclofenac. The higher dose of vitamin B₆ resulted in a larger effect. The effect of vitamin B₆ supplementation was seen as early as one day after the treatment and was still seen one week after initiation of the supplementation regimen.

EXAMPLE 4

The experiments reported in Example 3 were essentially repeated using a different set of essentially the same animals, but substituting indomethacin at the same amounts, for diclofenac. Each experiment used 1.5 times vitamin B₆ supplement. The results are given in Table 2, corresponding to the previous Tables.

TABLE 2

Group	0 Day on Diet			1 Day on Diet			7 Days of Diet		
	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)
1	437 ± 8	149 ± 2	320 ± 12	-	150 ± 2	320 ± 15	467 ± 8	149 ± 1	325 ± 11
2	480 ± 24	150 ± 1	320 ± 12	-	150 ± 1	340 ± 19	411*± 10	150 ± 2	331 ± 12
3	480 ± 17	148 ± 2	325 ± 11	-	134*± 1	335 ± 6	521 ± 16	132*± 5	355 ± 15
4	452 ± 7	148 ± 1	340 ± 10	-	124*± 2	350 ± 18	408 ± 2	116*± 1	344 ± 6

*P<0.05 with respect to normal chow or normal chow plus Indomethacin (100 mg/kg diet)

These results are comparable to those reported in Table 1(a).

Vitamin B₆ supplementation decreased the SBP of rats. This was quite significant in rats getting indomethacin, in addition.

EXAMPLE 5

In these experiments, the effects of the vitamin B₆ supplement (2.5 times the daily requirement) on the SBP of the older rats on commercial rat ration but receiving acetyl salicylate (20 or 100 mg per kg. diet) in the diet were investigated. The experiments were conducted as described in Example 1. Different sets of essentially the same animals were used. Table 3(a) reports the results with animals of four groups.

Group 1 was fed normal chow.

Group 2 was fed normal chow.

Group 3 was fed chow with 2.5 x vitamin B₆.

Group 4 was fed chow with 2.5 x vitamin B₆ plus acetylsalicylate (20 mg/kg diet).

Each Value is the Mean \pm S.E.M. of 5 rats.

TABLE 3 (a)

Group	0 Day on Diet			1 Day on Diet			7 Days of Diet		
	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)
1	443 ± 13	150 ± 1	330 ± 9	-	150 ± 2	330 ± 12	450 ± 10	150 ± 2	325 ± 10
2	450 ± 11	150 ± 2	325 ± 11	-	150 ± 3	300 ± 12	416*± 14	149 ± 1	315 ± 6
3	443 ± 21	148 ± 1	330 ± 9	-	137*± 1	335 ± 10	456 ± 16	132*± 1	300 ± 8
4	453 ± 13	149 ± 2	345 ± 5	-	124*± 1	355 ± 15	367 ± 8	116*± 1	340 ± 10

*P < 0.05 with respect to normal chow or normal chow plus acetylsalicylate

Table 3 (b) reports similarly the results of experiments in which the Group 2 and Group 4 animals received 100 mg/kg acetylsalicylate instead of 20 mg/kg - otherwise the experiments were the same.

Table 3 (b)

Group	0 Day on Diet			1 Day on Diet			7 Days of Diet		
	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)	B.Wt. (g)	SBP (mm Hg)	HR (beat /min)
1	560 ± 10	149 ± 1	345 ± 10	-	149 ± 1	340 ± 10	-	149 ± 1	350 ± 10
2	558 ± 15	148 ± 2	350 ± 10	-	148 ± 1	350 ± 15	-	148 ± 1	350 ± 10
3	565 ± 10	148 ± 1	345 ± 10	-	136*± 1	345 ± 10	-	133*± 1	350 ± 11
4	555 ± 12	148 ± 1	350 ± 10	-	125*± 1	340 ± 10	-	123*± 1	350 ± 12

*P < 0.05 with respect to normal chow or normal chow plus acetylsalicylate.

As in the previous experiments, vitamin B₆ supplementation decreased the SBP of these rats. The effects were most significant in rats receiving the anti-inflammatory

drug.

EXAMPLE 6

The effect of diclofenac administration with and without co-administration of vitamin B₆ was studied in young hypertensive rats as described in Example 3, but using a daily dosage of diclofenac of 10 mg/kg and continuing the treatment for 60 days. As before, four groups of rats were used, each group comprising 6 animals. Group 1 received a normal commercial chow ration daily. Group 2 received the same chow ration daily, supplemented with the diclofenac. Group 3 received the same chow ration daily, supplemented with 25 mg/kg vitamin B₆. Group 4 received the same chow ration daily, supplemented with both diclofenac and vitamin B₆ at the aforesaid amounts. The results are given below in Table 4.

TABLE 4

Group	Day 0		Day 60	
	Body wt (g)	SBP	Body wt	SBP
1	255±12	121±2	502±10	151±3
5 2	272±14	125±1	512±12	169±2
3	267±14	131±2	497±16	123±2
4	258±13	127±1	676±13	138±1

n=6, P<0.05 compared to Group 1 and Group 2, P<0.05
10 compared to Groups 1, 3 and 4.

The results reported in connection with these
Examples lead to the conclusion that moderate vitamin B₆
deficiency causes a modest hypertension in mammals. The
administration (i.p.) of non-steroidal anti-inflammatory
15 drugs exacerbates the hypertension in acute experiments.
Administration of vitamin B₆ or said derivative thereof
attenuates the hypertensive potential of the NSAIDs. In
longer term experiments the oral administration of a
vitamin B₆ (or derivative) supplement to older mammals
20 results in a significant decrease in the SBP of these
mammals which were still receiving NSAIDs. The co-
administration of vitamin B₆ (or derivative) and NSAIDs
results in a significant decrease in the SBP of older
mammals.

25 All references, including any patents or patent
applications, cited in this specification are hereby
incorporated by reference. No admission is made that any
reference constitutes prior art. The discussion of the
references states what their authors assert, and the
30 applicants reserve the right to challenge the accuracy and
pertinency of the cited documents. It will be clearly
understood that, although a number of prior art
publications are referred to herein, this reference does
not constitute an admission that any of these documents
35 forms part of the common general knowledge in the art, in
Australia or in any other country.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Use of vitamin B6 or a derivative thereof in the preparation of a medicament for use in the treatment of hypertension in a patient having hypertension and under treatment by one or more NSAIDs.
2. Use of claim 1, wherein the vitamin B6 derivative is a pharmaceutically acceptable form of pyridoxine.
3. Use of claim 2, wherein the pharmaceutically acceptable form of pyridoxine is pyridoxine hydrochloride addition salt.
4. Use of any one of claims 1 to 3, wherein the vitamin B6 derivative is selected from the group consisting of pyridoxal-5-phosphate, pyridoxal, pyridoxamine and 4-pyridoxic acid.
5. Use of any one of claims 1 to 4, wherein the NSAID is selected from the group consisting of indomethacin, an anti-inflammatory acetylsalicylate, naproxen, diclofenac, sulindac, alclofenac, amfenac, fenoprofen, ibuprofen, ketoprofen, flurbiprofen, alminprofen, ketorolac, GOBAB, amixetrine, diflunisal, and mefenamic acid.
6. Use of claim 5, wherein the NSAID is selected from the group consisting of diclofenac, indomethacin and an anti-inflammatory acetylsalicylate.
7. Use of claim 6, wherein the NSAID is diclofenac.
8. Use of claim 6, wherein the NSAID is indomethacin.

9. Use of claim 6, wherein the NSAID is an anti-inflammatory acetylsalicylate.
- 5 10. Use of any one of claims 1 to 5, wherein the patient is under treatment by at least two NSAIDs selected from the group consisting of indomethacin, sulindac and piroxicam.
- 10 11. Use of any one of claims 1 to 10, wherein the medicament further includes a NSAID.
12. Use of any one of the claims 1 to 11, wherein the medicament contains an amount of vitamin B₆ or a
15 derivative thereof in the range of 10 to 500 mg.
13. Use of claim 11 or claim 12, wherein the medicament further includes an NSAID in the range of 25 to
20 1000 mg.
14. A method of treating hypertension comprising the step of administering to a patient under treatment by one or more NSAIDs and in need thereof, an effective amount of vitamin B₆ or a derivative thereof.
25
15. A method of claim 14, wherein the vitamin B₆ derivative is a pharmaceutically acceptable form of pyridoxine.
- 30 16. Use of claim 15, wherein the pharmaceutically acceptable form of pyridoxine is pyridoxine hydrochloride addition salt.
17. Use of any one of claims 14 to 16, wherein the
35 vitamin B₆ derivative is selected from the group

consisting of pyridoxal-5-phosphate, pyridoxal, pyridoxamine and 4-pyridoxic acid.

18. Use of any one of claims 14 to 17, wherein the
5 NSAID is selected from the group consisting of
indomethacin, an anti-inflammatory acetylsalicylate,
naproxen, diclofenac, sulindac, alclofenac, amfenac,
fenoprofen, ibuprofen, ketoprofen, flurbiprofen,
alminprofen, ketorolac, GOBAB, amixetrine, diflunisal, and
10 mefenamic acid.

19. Use of claim 18, wherein the NSAID is selected
from the group consisting of diclofenac, indomethacin and
an anti-inflammatory acetylsalicylate.
15

20. Use of claim 19, wherein the NSAID is diclofenac.

21. Use of claim 19, wherein the NSAID is
indomethacin.
20

22. Use of claim 19, wherein the NSAID is an anti-
inflammatory acetylsalicylate.

23. Use of any one of claims 14 to 18, wherein the
25 patient is under treatment by at least two NSAIDs selected
from the group consisting of indomethacin, sulindac and
piroxicam.

24. Use of any one of claims 14 to 23, wherein the
30 medicament further includes a NSAID.

25. Use of any one of claims 14 to 24, wherein the
medicament contains an amount of vitamin B6 or a
derivative thereof in the range of 10 to 500 mg.
35

26. Use of claim 24 or claim 25, wherein the medicament further includes an NSAID in the range of 25 to 1000 mg.

5 27. Use in preparation of a medicament for treating hypertension in a mammalian patient caused by treatment of the patient with one or more NSAIDs, of a vitamin B₆ (or derivative) supplement selected from pyridoxine, pyridoxine hydrochloride, pyridoxal, pyridoxal-5-
10 phosphate, pyridoxamine and 4-pyridoxic acid.

28. Use of claim 27, wherein the NSAID is selected from the group consisting of indomethacin, and anti-inflammatory acetylsalicylate, naproxen, diclofenac,
15 sulindac, alclofenac, amfenac, fenoprofen, ibuprofen, ketoprofen, flurbiprofen, alminprofen, ketorolac, GOBAB, amixetrine, diflunisal and mefenamic acid.

29. Use in preparation of a medicament for treating
20 hypertension in a mammalian patient, of both an NSAID and a vitamin B₆ (or derivative) supplement selected from pyridoxine, pyridoxine hydrochloride, pyridoxal, pyridoxal-5-phosphate, pyridoxamine and 4-pyridoxic acid.

25 30. Use of claim 29, wherein the NSAID is selected from the group consisting of indomethacin, an anti-inflammatory acetylsalicylate, naproxen, diclofenac, sulindac, alclofenac, amfenac, fenoprofen, ibuprofen, ketoprofen, flurbiprofen, alminprofen, ketorolac, GOBAB,
30 amixetrine, diflunisal and mefenamic acid.

31. Use of claim 1, substantially as herein described with reference to any of the examples.

35 32. A method of claim 14, substantially as herein

described with reference to any of the examples.

33. Use of claim 27 or claim 29 , substantially as herein described with reference to any of the examples.

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