Modification of controlled hypotension induced by nicardipine or nitroprusside in cats pretreated with injectable acetyl salicylic acid

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ABSTRACT:
Controlled hypotension is a well established technique to decrease blood loss and improve surgical visibility. Several different pharmacologic agents have been used for controlled hypotension including direct acting vasodilators such as sodium nitroprusside and calcium channel blockers (Testa and Tobias, 1995). This study was designed to assess the effect of non-steroidal anti-inflammatory drug (NSAID) acetyl salicylic acid (ASA) therapy on the efficacy and safety of I.V. infusion of nicardipine compared with the more commonly used agent; sodium nitroprusside. The effect of each drug on blood pressure and ECG pattern of normal "control" cats and cats pretreated with (ASA) was investigated. A target mean arterial pressure (MAP) of 55-65 mmHg was to be achieved.

It was found that both nicardipine and nitroprusside achieved a stable controlled hypotensive state in control groups. Comparison between the two drugs revealed a significant increase in (MAP) with nitroprusside after drug discontinuation. Pretreatment with (ASA), attenuated significantly the effect of nicardipine infusion on (MAP). However, pretreatment with ASA produced insignificant effect on the decrease in MAP caused by nitroprusside except at 4 min. during infusion where ASA pretreatment attenuated its effect. Moreover (ASA) pretreatment decreased nitroprusside dose needed to reach the target blood pressure and increased time of blood pressure to return to base line.

Both nicardipine and nitroprusside infusion caused increase in mean heart rate (HR) without ECG changes in control and pretreated groups. There was a Statistically significant increase in (HR) in the (ASA) pretreated groups of both drugs when compared to that in the control groups. When the increase in (HR) induced by nitroprusside infusion was compared to that induced by nicardipine infusion, there was insignificant difference in the control groups, while in (ASA) pretreated groups the difference was significant.

INTRODUCTION:
One of the commonly used technique to limit blood loss and the possibility of transmitting infectious diseases in orthopedic surgical procedures is controlled hypotension. Controlled hypo-tension; referred to as deliberate or induced hypotension, is defined as a lowering of mean arterial pressure (MAP) below 55 mmHg or a decrease in (MAP) by one third or more from baseline values (Yaster et al., 1986). They used (MAP) as the determinant of the level of hypotension because it sets the lower limit of

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autoregulation in most organs, particularly the brain. Controlled hypo-
tension, is usually achieved by the use of a potent vasodilator with pred-
ictable, easily reversible effects. Sodium nitroprusside, is often used for this
purpose despite the potential disad-
evantages of cyanide toxicity, reflex
tachycardia, and rebound hypertension (Bloor et al., 1985). Nicardipine is an
intravenously administered dihydropy-
ridine calcium channel antagonist. Its
primary physiologic action is arterial
vasodilation with limited chronotrophic,
dromotropic, and ionotropic effects (Frishman, 1989). Its distribution and
elimination half life is short and this
allow for rapid titration of blood pres-
sure (Turlapaty et al., 1989).

During the past 25 years, (NSAIDs), have become one of the
most frequently prescribed classes of
medication. Concurrent use of
(NSAIDs), in non arthritis conditions
for both short and long term, may
approach million of patients (Houston,1991).

Recently, there has been a
growing awareness and concern that
most of (NSAIDs) are additionally
capable of affecting blood pressure
(Klassen et al., 1995). So, this work was
designed to assess and evaluate the
effect of pretreatment with (ASA), on
controlled hypotension induced by
nicardipine or nitroprusside.

MATERIALS AND METHODS

Drugs used in this study
were: nicardipine hydrochloride
(Cardene, I.V.I, Syntex U.S.A),
sodium nitroprusside dihydrate
(Nipride I.V.I, warwick U.K. "Sensitive
to light"), and
acetyl salicylic acid (Aspegic injec-
table, Amriya).

Doses corresponding to human ther-
peutic doses were calculated according to the method reported by

Paget and Barnes (1964), and
statistical analysis of the data was
performed by student "t" test of
significance.

Mean arterial pressure (MAP) =
diastolic + (systole-diastol)/3 mmHg.
Heart rate (beats/min) was also calcu-
lated from the recorded ECG.

Experiment design:

Four groups of cats, each of six
animals were used. The first group was
treated with intravenous infusion
(I.V.I.) of nicardipine (10 ug/kg/min.),
and the second group with I.V.I. of
sodium nitroprusside (lug/kg/min.).
Both infus -ions were titrated as needed
to ach -ive the target (MAP) of 60
mmHg (55-65 mmHg). Information
collected for both drugs included
before, during, at the end of
infusion, and after 10,20 mins. Of drug
discontinuation. Drug requirement
(ug/kg), and the time needed for B.P. to
return to baseline values were also
recorded. ECG (lead II) at baseline
before hypotension, dur -ing the B.P. of
55-65 mmHg, and 20 min. after drug
discontinuation, was recorded. These
two groups were consi -dered as control
groups.

The third and fourth groups were
pretreated with acetyl salicyclic acid
(Aspegic I.M.) 25 mg/kg/day for 7
days. At the end of treatment period,
animals in the third group were given
nicardipine, and the fourth group were
given nitroprusside in the same way
mentioned in the first and second
groups. The same parameters mentioned
above were recorded and compared
with that of the control groups.

RESULTS:

I. Effect of the drugs on mean
arterial blood pressure (MAP):

Control groups: Both nicardipine and
nitroprusside infusion induced a drop in
the MAP. Comparison between the
effect of the two drugs revealed a
significant increase in (MAP) with nitroprusside after drug infusion discontinuation compared to that with nicardipine infusion (Figs 1,2, Table I).

Fig. (1): Controlled hypotension induced by nicardipine 10 μg/kg/min. infusion in control cats.

Fig. (2): Controlled hypotension induced by nitroprusside 1 μg/kg/min. infusion in control cats.

**Acetyl salicylic acid pretreated groups:** Pretreatment with (ASA) attenuated the effect of nicardipine on (MAP). This attenuation was statistically significant, compared to that of control group. Comparison between the effect of nicardipine and nitroprusside infusions in (ASA) pretreated groups, showed a statistically significant decrease in (MAP) with nitroprusside during and at the end of infusion (Figs. 3,4, Table I).
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Fig. (3): Controlled hypotension induced by nicardipine 10 μg/kg/ min. infusion in ASA pretreated cats.

Fig. (4): Controlled hypotension induced by nitroprusside 1 μg/kg/ min. infusion in ASA pretreated cats.
Table (1): Effect of pretreatment with acetyl salicylic acid (Aspegic I.M. 25 mg/kg/day for 7 days) on controlled hypotension induced by nicardipine (10 ug/kg/min.) or nitroprusside (1 ug/kg/min) infusion.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Before infusion</th>
<th>During infusion</th>
<th>At end of infusion</th>
<th>After drug discontinuation</th>
<th>Range of drug requirement to achieve target MAP (ug/kg)</th>
<th>Time needed for BP to return to base line (min.)</th>
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<td>2 min.</td>
<td>4 min.</td>
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<td>Nicardipine:</td>
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<td></td>
<td>92.4 ± 7.66</td>
<td>69.3±2.96</td>
<td>62.1±2.38</td>
<td>55.5±1.23</td>
<td>57.9±0.95</td>
<td>64.4±2.39</td>
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<td>18 - 75</td>
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<td></td>
<td>84.8 ± 2.18</td>
<td>65.8±3.26</td>
<td>58.6 ± 0.87</td>
<td>53.6 ± 0.98</td>
<td>61 ±1.84</td>
<td>84.6 ±4.60*</td>
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<td>99.4 ±2.79*</td>
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<td><strong>ASA Pretreated groups</strong></td>
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<td>Nicardipine:</td>
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<td>91.1 ± 7.35</td>
<td>86.8±5.82†</td>
<td>80.9 ± 4.80†</td>
<td>73.4 ± 1.03†</td>
<td>75 ± 2.24†</td>
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<td>86 ± 3.67</td>
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<td>Nitroprusside:</td>
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<td>106 ± 6.78*</td>
<td>71.8±1.83*</td>
<td>63.6±0.98**</td>
<td>54.4±1.17*</td>
<td>62.6±1.94*</td>
<td>84±4.85</td>
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<td>98.4±6.64</td>
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<td>8-13</td>
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</table>

* Significant difference between the effect of nitroprusside and nicardipine in control and (ASA) pretreated groups.
† Significant difference in the effect of nicardipine in (ASA) pretreated group when compared to that in control group.
* Significant difference in the effect of nitroprusside in (ASA) pretreated group when compared to that in control group.

II. Effect of drugs on ECG:

Reflex increase in mean heart rate (HR) when compared to that in the control groups. The increased (HR) with nitroprusside infusion was statistically insignificant (P>0.05) in control group and significant in (ASA) pretreated group when compared to that with nicardipine infusion.

Table (2): Effect of pretreatment with acetyl salicylic acid (Aspegic IM 25 mg/kg/day/7 days). On heart rate (HR) beats/min (mean ± SEM) caused by nicardipine (10 ug/kg/min.) or nitroprusside (1 ug/kg/min) infusion.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Initial (HR)</th>
<th>(HR) during target mean arterial pressure</th>
<th>(HR) after 20 min of drug discontinuation</th>
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<tr>
<td>Control group</td>
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<tr>
<td>Nicardipine</td>
<td>160 ± 7.07</td>
<td>177 ± 7.07</td>
<td>177 ± 7.07</td>
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<tr>
<td>Nitroprusside</td>
<td>160 ± 7.07</td>
<td>200 ± 7.07</td>
<td>177 ± 7.07</td>
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<td>(ASA) pretreated groups:</td>
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<tr>
<td>Nicardipine</td>
<td>200 ± 7.07*</td>
<td>228 ± 7.07*</td>
<td>228 ± 7.07*</td>
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<tr>
<td>Nitroprusside</td>
<td>228 ± 7.07↑*</td>
<td>266 ± 7.07↑*</td>
<td>228 ± 7.07↑</td>
</tr>
</tbody>
</table>

* Significant difference between the effect of nicardipine in (ASA) pretreatment group when compared to that in control group.
† Significant difference between the effect of nitroprusside in (ASA) pretreatment group when compared to that in control group.
* Significant difference between the effect of nitroprusside in (ASA) pretreatment group when compared to that of nicardipine pretreated group.
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DISCUSSION:

Because arthritis and hypertension are conditions that frequently occur together, there is a large population of patients for whom the concurrent use of antihypertensive and NSAIDs is indicated. The NSAIDs attenuate the antihypertensive actions of most antihypertensive drug classes. The effect on blood pressure can vary from none to severe blood pressure elevation, depending on the NSAIDs used (Pope et al., 1993). Such interactions are of great clinical importance given the widespread use of NSAIDs and their "Over the Counter" availability. Most often, hypotension is induced by a potent vasoactive agent with predictable short life and easily reversible effects. For these reasons, nitroprusside remains very desirable although there is a risk of cyanide poisoning at doses > 1.5 mg/kg (Michenfelder and Tinker, 1977).

Short-term infusion of nicardipine; a water-soluble photoresistant dihydropyridine calcium channel blocker, also can be used to induce deliberate hypotension (Bernard et al., 1991).

The present study showed that the control groups receiving nicardipine and nitroprusside allowed a rapid achievement of hypotension. After discontinuation of the infusions nitroprusside induced a statistically significant increase in MAP and rapid recovery in comparison to nicardipine. This action shows conformity with the study of Bernard et al. (1991) who reported that, nicardipine was, as potent and as easy to use as nitroprusside in reducing arterial blood pressure. He also reported that rebound hypertension was observed after abrupt discontinuation of nitroprusside, resulting from persistent increased plasma renin activity and catecholamine levels. Tobias et al., (1996) also mentioned that, blood pressure rapidly returned to base line after nitroprusside discontinuation and a more prolonged effect was noted with nicardipine. The authors suggested that, the prolonged vasodilatory effect of nicardipine might be efficacious in that it prevented the rebound hypertension related to the elevated plasma renin activity and endogenous catecholamines that is sometimes seen with nitroprusside infusion. A possible explanation of the difference in time courses of the two drugs may also be found in their cellular mechanisms of action. Nitroprusside causes vascular relaxation via production of nitric oxide (NO), which has a half-life of 0.1 seconds. Removal of this (NO) donor would be expected to cause rapid restoration of BP (Hersey et al., 1997). Nicardipine, however, is a calcium channel blocker, and it interferes with calcium dependent regulatory mechanism of vascular smooth muscle tone. Removal of nicardipine would not result in restoration of baseline BP until the drug diffuses off the receptor site and normal intracellular calcium balance is restored (Dzau et al., 1993).

Pretreatment with (ASA), in the present study, attenuated significantly the effect of nicardipine infusion on (MAP). However, nitroprusside infusion caused a decrease in the (MAP), which was statistically significant compared to that of nicardipine effect. The proposed mechanism for NSAIDs attenuation of blood pressure effect, is related to blockade of cyclooxygenase pathway of arachidonic acid metabolism with a resultant decrease in the biosynthesis of all prostanoids (Pope et al., 1993). The prostaglandins are important in normal modulation of renal, glomerular and systemic vascular dilatation and sodium water balance.
(Paterno and Dunn, 1987). Inhibition of this system by NSAIDs may lead to renal vasoconstriction, reduction in glomerular filtration rate, increase in sodium and water resorption, intravascular volume overload, enhanced adrenergic neurotransmission, increased effects of angiotensin II, and vasopressin, and increased intravascular volume with increased systemic vascular resistance, resulting in substantial elevation in blood pressure. Unless the antihypertensive drug maintains its efficacy in the presence of such changes (Houston et al., 1995). Recently, Foegh and Ramell (2001) reported also that prostaglandin synthase (cyclooxygenase) is not needed for the formation of isoprostanes; prostaglandin stereoisomers. The importance of this pathway lies in the large amounts of these products, and their potent vasoconstrictor effects in the vascular beds. The same authors found that aspirin should not affect the isoprostane pathway.

Calcium channel blockers are known to have direct vasodilatory effects on resistance vessels and this is likely their major antihypertensive mechanism. They also have clearly shown that they have a natriuretic effect (Weinberger, 1991). This natriuretic effect on the circulation as reported by Levin et al. (1998). Despite of this natriuresis, Houston et al., (1995) found that, the NSAIDs; ibuprofen and naproxen, in concomitant use with sustained release verapamil hydrochloride, increased blood pressure significantly. Klassen et al., (1995) stated insignificant increase in blood pressure when naproxen was added to nicardipine therapy. A few clinical reports, on the other hand, have suggested that NSAIDs, do not attenuate the antihypertensive effects of calcium channel blockers (Houston, 1991).

The failure of NSAIDs to compete with nitroprusside effect on blood pressure was explained by the varying effects of these antihypertensive agents. Nitroprusside causes vascular relaxation via production of nitric oxide which results in increased cGMP synthesis and smooth muscle relaxation (Bernard et al., 1991). Direct vasodilation due to nitroprusside may compete with vasoconstriction produced by ASA increasing autonomic activity, catecholamine secretion, and angiotensin II activation (Knight et al.,1983). In addition, it may be explained by arterial and venous effects of nitroprusside in contrast to the vasodilatory effect of nicardipine which is most probably an arterial effect (Bernard et al., 1991).

With regards to the effect of both nicardipine and nitroprusside infusions on the ECG of cats, both drugs exhibited reflex increase in mean heart rate without changing the ECG pattern. This increase was statistically significant in (ASA) pretreated groups receiving nicardipine or nitroprusside in comparison to control groups receiving the same drugs. The increased heart rate due to nitroprusside was higher than that due to nicardipine in control (insignificant) and in (ASA) pretreated (significant) groups. This tachycardia can be explained by an acute activation of the baroreflex control mechanism, which follows the blood pressure and buffers it around the new level of set point (Young et al.,1984). Previous reports have indicated that, nicardipine results in less reflex tachycardia than nitroprusside (The IV nicardipine study group, 1991). Hersey et al. (1997) reported also that, although more patients in the nitroprusside group required esmolol, the reflex
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tachycardia was not statistically significant. Studies in adults comparing nicardipine with nitroprusside for intraoperative and postoperative hypertension, demonst rated also a significant smaller increase in heart rate with nicardipine than with nitroprusside (Halpern et al., 1992). The positive chronotropic pattern of (ASA) pretreated groups, seems to be due to the vasoconstriction produced by (ASA) increasing autonomic activity, catecholamine secretion and angiotensin II activation as previously explained by Knight et al., (1983).

In this study it was concluded that, controlled hypotension can be easily achieved by nicardipine infusion. Moreover there is a beneficial slow gradual return to baseline blood pressure in comparison to the rebound hypertension and reflex tachycardia induced by nitroprusside infusion. Non steroidal anti-inflammatory "acetylsalicylic acid" regimens, used in this study attenuated significantly the hypotensive effect caused by nicardipine. Nitroprusside was Uniformly effective. In addition (ASA) pretreatment decreased nitroprusside dose needed to reach the target blood pressure, and increased the time needed for the blood pressure to return to baseline. Therefore, nitroprusside appears to be the agent of choice for rapid induction of controlled hypotension in Patients who are taking Concomitant long-term acetylsalicylic acid therapy.

REFERENCES:


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التحوير في خفض الضغط المقنَّن المُحدثُ بواسطة النييكلاربيين أو الصوديوم

نيتريبوروسيد في القطر المسبق ماعاجتها بحفل حمض الاستيل سالسيليك

منى محمد رضوان
قسم الفارماكولوجى - كلية طب البنات
جامعة الأزهر - القاهرة

أجرى هذا البحث لمعرفة تأثير حمض الاستيل سالسيليك على فاعلية النييكلاربيين أو
الصوديوم نيتريبوروسيد المُحدثُ لخفض الضغط المقنَّن في القطر.

استخلص من هذا البحث أن خفض الضغط المقنَّن ممكن إحداثه بطريقة سهلة بواسطة
إدخال "تسريب" النييكلاربيين في الوريد. علاوة على ذلك هناك فائدة من الجروح البطىء في ضغط
الدم إلى الضغط المبدئي بواسطة النييكلاربيين بالمقارنة بارتفاع ضغط الدم وسرعة ضربات القلب
المُحدثُ كرد فعل لاستخدام النيتريبوروسيد.. وذلك في القطر المستخدمة كمرجع.

أما عند حفن حمض الاستيل سالسيليك المسبق لاستخدام النييكلاربيين أو النيتريبوروسيد...
فقد بينت التجارب أن حمض الاستيل سالسيليك قد أحدث تثبيت في فاعلية خفض الضغط المقنَّن
المحدث بواسطة النييكلاربيين. أما النيتريبوروسيد.. فقد كان بنفس التأثير والكفاءة... وبالإضافة إلى
ذلك فقد حدد خفض في كمية النيتريبوروسيد المطلوبة للوصول إلى الضغط المنخفض.. وكذلك
حدث زيادة في الوقت المطلوب للعودة بضغط الدم إلى المستوى المبدئي.

من هذا يتضح أن الصوديوم نيتريبوروسيد هو الدواء المطلوب لإحداث خفض ضغط دم
مقنَّن ذو فاعلية في الحالات التي سبق استخدامها لحمض الاستيل سالسيليك.