Counter-Regulatory Responses to Continuous and Intermittent Therapy With Nitroglycerin

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Background. Vasodilator therapy may be associated with reflex counter-regulatory responses, and these responses may play a role in the development of tolerance to nitroglycerin (GTN).

Methods and Results. Standing systolic blood pressure, body weight, urinary sodium, and hormonal responses to continuous \((n=10)\) and intermittent \((n=10)\) transdermal GTN administration were studied in normal volunteers. There was rapid attenuation of the hypotensive response to transdermal GTN therapy in the continuous but not in the intermittent therapy group. Significant weight gain and sodium retention occurred during continuous but not during intermittent GTN therapy. This was accompanied by a greater decrease in hematocrit in the continuous group, a finding that suggests that plasma volume expansion occurred during continuous GTN therapy. Continuous GTN therapy was associated with increases in plasma norepinephrine, atrial natriuretic peptide, arginine, vasopressin, and plasma renin activity. A different pattern of neurohormonal response was seen during intermittent therapy, with values tending to return to baseline levels after the nitrate-free interval.

Conclusions. Continuous transdermal GTN therapy leads to counter-regulatory responses associated with sodium retention and probable plasma volume expansion. By contrast, intermittent transdermal GTN therapy is associated with a different pattern of hormonal response, the lack of sodium retention and no evidence of plasma volume expansion. It is likely that these counter-regulatory responses play an important role in the attenuation of nitrate effects. (Circulation 1991;84:2336–2345)

The organic nitrates are widely used in the management of angina pectoris and congestive heart failure. Despite their broad use, it is now recognized that during sustained therapy, the effects of nitrates become substantially diminished. Several investigations have demonstrated rapid attenuation of both the hemodynamic and antianginal effects of oral, topical, and intravenously administered nitrates.\(^1\)\(^–\)\(^10\) The basis of nitrate tolerance is not completely understood. Most investigations have focused on the mechanisms underlying nitrate-mediated vascular dilatation and the theory that nitrate tolerance occurs because of depletion of reduced sulfhydryl groups in vascular smooth muscle.\(^1\)\(^1\) Recently, there has been increasing evidence that reflex neurohormonal responses during nitrate therapy may be involved in the attenuation of nitrate effects. Some studies have demonstrated that therapy with organic nitrates is associated with heightened sympathetic tone and activation of the renin-angiotensin system.\(^1\)\(^2\),\(^13\) It has been suggested that resulting vasoconstriction, when combined with an increase in plasma volume,\(^1\)\(^4\) may serve to blunt the potent hemodynamic effects seen during acute nitrate administration.

In this investigation, we evaluated the effects of continuous and intermittent therapy with transdermal nitroglycerin (GTN) in a group of normal subjects. We hypothesized that the continuous administration of GTN would be associated with release of endogenous vasconstrictors and retention of sodium and water. A second hypothesis was that the intermittent therapy with GTN would prevent sustained neurohormonal activation, limit sodium and water retention, and thus allow for continued nitrate effects.

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Methods

Subjects

The study population consisted of 20 normal volunteers. There were 18 men and two women; ages ranged from 21 to 31 years. There was no history of renal or cardiac disease. All subjects had a normal physical examination, electrolytes, blood urea nitrogen, creatinine, hematocrit, and urinalysis. None of the subjects were taking medications at the time of the investigation.

The study protocol was approved by the ethics committee of Queen’s University, Kingston, Ontario, Canada and written informed consent was obtained in all cases.

Out-of-Hospital Phase

Subjects were initially seen as outpatients, at which time they had a screening medical history and physical examination. During this visit, they also underwent a GTN dose titration. Each subject initially received a GTN patch delivering 10 mg/24 hours (Transderm Nitro, CIBA-GEIGY Corporation) and standing blood pressure was monitored every 10 minutes for the next 2 hours. The aim was to achieve a 10–20 mm Hg fall in systolic blood pressure without going below 90 mm Hg. If an adequate blood pressure response was not achieved after 2 hours with the single GTN patch, further 10-mg units were applied at 30-minute intervals until this was achieved. The maximum dose applied was 40 mg/24 hours. The dose determined during this titration was subsequently used during the in-hospital phase of the investigation. Finally, each subject was interviewed by a dietitian and their average caloric and sodium intake was estimated.

In-Hospital Phase

Subjects were admitted to the Special Investigation Unit of the Kingston General Hospital for a 7-day period. Throughout their hospital stay, they received a diet of known caloric, water, sodium, potassium, and calcium content. On the basis of their usual dietary intake, they were prescribed a diet designed to maintain their normal caloric and sodium intake. They ate identical meals each day and were instructed to eat everything provided. Subjects were asked to remain on the ward and refrain from all vigorous exercise for the duration of their hospital stay.

Study Protocol

During the first 4 days of hospitalization no therapy was given, as this period was designed to allow subjects to achieve sodium and water balance. Throughout the hospitalization, 24-hour urine collections were carried out for determination of urinary sodium output. Subjects were weighed daily before breakfast at 8 AM and 8 PM using the same hospital balance scale. Starting on the morning of hospital day 3, heart rate and blood pressure measurements were made at 8 AM, 10 AM, noon, and 4 PM. Heart rate and blood pressure were recorded after the subject had been standing quietly for 5 minutes. Blood pressure was measured by trained personnel using a sphygmomanometer. Three separate measurements separated by 1 minute were made and the results averaged. Heart rates were determined from a 1-minute count of the pulse.

During the evening of day 3, an 18-gauge heparin lock was established in the nondominant forearm of each subject to allow venous blood sampling. On days 4–7 at 8 AM, 10 AM, noon, and 4 PM, blood was drawn to determine plasma renin activity, levels of plasma norepinephrine, epinephrine, aldosterone, arginine vasopressin, and atrial natriuretic peptide. On these same days, hematocrit was measured at 8 AM and 8 PM. All blood samples were drawn after the subject had been standing quietly for 10 minutes.

Transdermal GTN Administration

Therapy with transdermal GTN was begun on day 5. Two different transdermal dosing regimens were used. Ten subjects underwent continuous therapy and the remaining 10 received an intermittent treatment regimen. In both cases, GTN patches were applied at 8 AM shortly after morning measurements were complete. In the continuous group, patches were left in place for 24 hours and reapplied each morning. In the intermittent group, the patches were removed each day at 8 PM.

Hormonal Measurements

Plasma catecholamine levels were determined by the method of Peuler and Johnson.\textsuperscript{15} Using this method, the intra- and interassay variation for norepinephrine are 8% and 15%, respectively, whereas for epinephrine they are 15% and 31%, respectively. Plasma renin activity was determined using a radioimmunoassay with an intra- and interassay variation of 8% and 14%, respectively, according to the method of Emanuel.\textsuperscript{16} Aldosterone levels were determined using the method of Mayes et al,\textsuperscript{17} an assay with an intra-assay variation of 4% and an interassay variation of 11%. Arginine vasopressin levels were determined using a radioimmunoassay with a sensitivity of 0.06 nmol per sample, an intra-assay variation of 7%, and an interassay variation of 10%. Atrial natriuretic peptide was assayed using a radioimmunoassay with an intra-assay variation of 4% and an interassay variation of 9%, according to the method of Sarda and deBold.\textsuperscript{18}

Statistical Methods

All data are presented as mean±SEM. Heart rate, blood pressure, and hormonal data were analyzed by means of a repeated-measures analysis of variance, with days and hours as within-subjects effects. This design yielded tests of whether: 1) mean values on these measurements varied significantly across days, 2) whether they exhibited a diurnal pattern resulting in significant differences across hours, and 3) whether the daily effect varied as a function of the
Continuous Therapy

![Graph A](image1)

Intermittent Therapy

![Graph B](image2)

**Figure 1.** Standing systolic blood pressure (systolic BP; mm Hg) and standing heart rate in beats per minute (BPM) on the day before treatment with nitroglycerin (day 4) and on each of the three treatment days (days 5–7). Panels A and B: Continuous therapy. Panels C and D: Intermittent therapy. The numbers 8, 10, 12, and 16 on the X axis indicate 8 AM, 10 AM, noon, and 4 PM, respectively. Values are mean±SEM. *p<0.05 vs. 10 AM on day 4; †p<0.05 vs. noon on day 4; *p<0.05 vs. 4 PM on day 4.

hour at which values were measured. In cases where significant F values were found, specific preplanned comparisons between baseline and subsequent data points were performed with day 4 serving as baseline for the day effect and 8 AM serving as baseline for the hourly effect. Changes in body weight, hematocrit, and urinary sodium within each group were assessed by performing two-tailed paired t tests, whereas differences in the response of these variables between the two groups were analyzed by using two-tailed unpaired t tests. Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

**Results**

**Transdermal GTN Dosage**

The dose of GTN used was that determined from the dose titration carried out during the out-of-hospital phase. The mean GTN dosage in the continuous therapy group was 29±2 mg/24 hours and 29±3 mg/24 hours in the intermittent group.

**Heart Rate and Blood Pressure Responses**

In the continuous therapy group, administration of transdermal GTN was associated with a significant decrease in standing systolic blood pressure that persisted for 26 hours. Subsequent blood pressure values were unchanged compared with baseline values (Figure 1A). In the intermittent therapy group, patch application led to a significant decrease in systolic blood pressure from the 8 AM values on each day of therapy, although there was some attenuation of this response over time (Figure 1C).

Continuous GTN therapy was associated with a significant increase in standing heart rate that persisted for the 8-hour observation period after initial patch application. However, by 24 hours, heart rate was not different from the pretreatment values (Figure 1B). In the intermittent therapy group, there was a significant increase in heart rate after patch application on each of the three treatment days (Figure 1D).

**Body Weight, Urinary Sodium, and Hematocrit Responses**

During the first 48 hours of GTN therapy, the continuous therapy group gained 1.0±0.2 kg (p=0.0001), whereas the intermittent therapy group gained only 0.3±0.2 kg (p=0.2). The weight gain during continuous therapy was significantly greater in the continuous therapy group than in the intermittent therapy group (p<0.01).
In the continuous therapy group, there was a significant decrease in 24-hour urinary sodium with the initiation of therapy. Thus, on days 3 and 4, before the initiation of therapy, the mean 24-hour urinary sodium was 128±12 mmol/24 hours, whereas during the first two days of GTN therapy, this value fell to 79±6 mmol/24 hours (p=0.002; Table 1). Values for urinary sodium are not available for day 7, the final day of GTN therapy, because subjects were discharged from the hospital in the late afternoon. During therapy with intermittent GTN there was only a small, nonsignificant decrease in urinary sodium during the same period (Table 1). The decrease in urinary sodium that occurred in the continuous therapy group was greater than in the intermittent therapy group (49±12 mmol/24 hours versus 10±5 mmol/24 hours; p=0.004).

The hematocrit decreased 0.046±0.004 l/l in the constant therapy group and 0.021±0.004 l/l in the intermittent therapy group (p<0.001 for both; Table 1). The decrease in the constant therapy group was significantly greater than the decrease in the intermittent therapy group (p<0.001).

**Hormonal Responses**

All baseline catecholamine and hormonal values were within the normal range. In the continuous therapy group, there was a significant increase in the mean daily value of plasma norepinephrine on the first and third days of therapy (p<0.05; day 5 and 7 versus day 4; Figure 2A and Table 2). The interaction of days and hours in this case yielded no evidence that this effect varied significantly as a function of the hour of the day (Figure 2B). In the intermittent therapy group, each patch application was followed by a significant increase in the mean daily value of plasma norepinephrine (Figure 2C; Table 3). In this group, there was also a significant hourly effect. Each patch application was followed by a significant increase in plasma norepinephrine; however, on days 6 and 7, the second and third treatment day, norepinephrine values returned to baseline at 8 AM after the 12-hour nitrate-free interval (Figure 2D).

The increase in mean plasma epinephrine levels that occurred during continuous therapy with GTN was not significant. By contrast, during intermittent therapy there was a significant increase in epinephrine values on each day of therapy (Table 3). In this case, the hourly effect was not significant; thus, this increase did not appear to vary significantly as a function of hours of the day.

Plasma renin activity, expressed as mean daily values, became significantly elevated on days 5 and 6 in the continuous therapy group. Levels on day 7, the third day of therapy, had returned to baseline values (Figure 3A; Table 2). Analysis of individual sample responses reveals that the interaction of hours and days is not significant; thus, the daily pattern of response seen at each hour of measurement is similar to that seen with the mean daily values (Figure 3B). Although there was an increase in plasma renin activity on the first day of therapy in the intermittent therapy group, this increase was of borderline statistical significance (p=0.07, day 4 versus day 5; Figure 3C and Table 3). Examination of Figure 3D reveals that during intermittent therapy, patch application was associated with a daily increase in plasma renin activity with a return to baseline values after the 12-hour nitrate-free period. However, the analysis of variance indicated that this pattern did not represent a statistically reliable finding.

Mean aldosterone levels demonstrated a small, statistically insignificant increase on the first day of GTN therapy. However, in both groups there was a significant decrease in mean aldosterone levels on day 7, the third day of GTN therapy (Tables 2 and 3).

In the continuous therapy group, mean daily values of atrial natriuretic peptide became elevated on day 6, the second day of therapy (Figure 4A; Table 2). Analysis of individual sample values reveals that this effect did not vary significantly as a function of the hour of the day (Figure 4B). With intermittent therapy, there was no significant change in the mean

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**TABLE 1. Effect of Continuous and Intermittent Nitroglycerin Therapy on Body Weight, Hematocrit, and Urinary Sodium**

<table>
<thead>
<tr>
<th></th>
<th>Continuous GTN therapy</th>
<th>Intermittent GTN therapy</th>
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</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td></td>
<td></td>
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<tr>
<td>Before GTN therapy</td>
<td>73.2±2.1</td>
<td>77.8±4.6</td>
</tr>
<tr>
<td>After 48 hours of GTN therapy</td>
<td>74.2±2.1*</td>
<td>78.1±4.5</td>
</tr>
<tr>
<td>Hematocrit (l/l)</td>
<td></td>
<td></td>
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<tr>
<td>Before GTN therapy</td>
<td>0.453±0.01</td>
<td>0.45±0.01</td>
</tr>
<tr>
<td>After 48 hours of GTN therapy</td>
<td>0.407±0.01*</td>
<td>0.429±0.01*</td>
</tr>
<tr>
<td>Urinary sodium (mmol/24 hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before GTN therapy</td>
<td>128±12</td>
<td>123±13</td>
</tr>
<tr>
<td>First 48 hours of GTN therapy</td>
<td>79±6*</td>
<td>113±15</td>
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GTN, nitroglycerin.
*p<0.01 vs. before GTN therapy.
daily value of atrial natriuretic peptide (Figure 4C, Table 3), however in this case there was a significant hourly effect with a distinct increase at the 8 AM value on day 6 and day 7 after the 12-hour nitrate-free interval (Figure 4D).

Plasma levels of arginine vasopressin increased in response to GTN therapy in both groups (Figure 5; Tables 2 and 3). In the continuous therapy group, mean daily values were elevated on the first and second day of therapy but returned to baseline by the final day of therapy (Figure 5A; Table 2). The interaction of days and hours in this case revealed no hourly effect; thus, the pattern seen with values taken at individual hours was not significantly different from that seen with the mean daily values (Figure 5B). During intermittent therapy, there was a slight

![Continuous Therapy Diagram](image1)

**Continuous Therapy**

![Intermittent Therapy Diagram](image2)

**Intermittent Therapy**

**Figure 2.** Plasma norepinephrine levels (ng/L) on the day before nitroglycerin therapy (day 4) and on each of the treatment days (days 5–7). Panel A: Mean daily plasma norepinephrine levels in the continuous therapy group. Panel B: Plasma norepinephrine levels at each sampling period in the continuous therapy group. Panel C: Mean daily plasma norepinephrine levels in the intermittent therapy group. Panel D: Plasma norepinephrine levels at each sampling period in the intermittent therapy group. The numbers 8, 10, 12, and 16 on the X axis indicate 8 AM, 10 AM, noon, and 4 PM, respectively. Values are mean±SEM; *p<0.05 vs. day 4; **p<0.05 vs. 10 AM on day 4; °p<0.05 vs. noon on day 4, °p<0.05 vs. 4 PM on day 4.

<table>
<thead>
<tr>
<th>Table 2. Mean Daily Hormonal Values for Continuous Therapy</th>
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<tr>
<td>Hospital day</td>
</tr>
<tr>
<td>NE (ng/l)</td>
</tr>
<tr>
<td>EPI (ng/l)</td>
</tr>
<tr>
<td>PRA (µg/l/hr)</td>
</tr>
<tr>
<td>Aldo (nmol/l)</td>
</tr>
<tr>
<td>ANP (ng/l)</td>
</tr>
<tr>
<td>AVP (ng/l)</td>
</tr>
</tbody>
</table>

GTN, nitroglycerin; NE, norepinephrine; EPI, epinephrine; PRA, plasma renin activity; Aldo, aldosterone; ANP, atrial natriuretic peptide; AVP, arginine vasopressin.

*p<0.05 vs. day 4.
TABLE 3. Mean Daily Hormonal Values for Intermittent Therapy

<table>
<thead>
<tr>
<th>Hospital day</th>
<th>GTN therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td>NE (ng/l)</td>
<td>229±13</td>
</tr>
<tr>
<td>EPI (ng/l)</td>
<td>36±4</td>
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<tr>
<td>PRA (µg/l/hr)</td>
<td>4.3±0.4</td>
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<tr>
<td>Aldo (nmol/l)</td>
<td>0.75±0.06</td>
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<tr>
<td>ANP (ng/l)</td>
<td>21±2</td>
</tr>
<tr>
<td>AVP (ng/l)</td>
<td>1.5±0.2</td>
</tr>
</tbody>
</table>

GTN, nitroglycerin; NE, norepinephrine; EPI, epinephrine; PRA, plasma renin activity; Aldo, aldosterone; ANP, atrial natriuretic peptide; AVP, arginine vasopressin.

*p<0.05 vs. day 4.

increase in the daily mean level of arginine vasopressin on day 5, with values on days 6 and 7 not significantly different from day 4 (Figure 5C; Table 3). Once again, examination of individual sample values revealed that there was no significant hourly effect (Figure 5D).

Discussion

Recently, there has been increasing interest in the concept that reflex, counter-regulatory responses may be partially responsible for the loss of effectiveness seen during sustained therapy with the organic nitrates. This study provides a detailed examination of the neurohormonal responses to therapy with transdermal GTN in subjects without congestive heart failure. The dose used in this investigation was high, some two to three times the dose typically used in the therapy of angina. Despite this large dose, attenuation of the hemodynamic response to transdermal GTN occurred rapidly in the continuous

Continuous Therapy

Intermittent Therapy

FIGURE 3. Plasma renin activity (PRA) in µg/L/hr on the day before nitroglycerin therapy (day 4) and on each of the treatment days (days 5–7). Panel A: Mean daily PRA in the continuous therapy group. Panel B: PRA at each sampling period in the continuous therapy group. Panel C: Mean daily PRA in the intermittent therapy group. Panel D: PRA at each sampling period in the intermittent therapy group. The numbers 8, 10, 12, and 16 on the X axis indicate 8 AM, 10 AM, noon, and 4 PM, respectively. Values are mean±SEM. **p<0.05 vs. day 4.
Continuous Therapy

![Graph A](image)

![Graph B](image)

Intermittent Therapy

![Graph C](image)

![Graph D](image)

FIGURE 4. Atrial natriuretic peptide (ANP) levels in ng/L on the day before nitroglycerin therapy (day 4) and on each of the treatment days (days 5-7). Panel A: Mean daily ANP in the continuous therapy group. Panel B: ANP at each sampling period in the continuous therapy group. Panel C: Mean daily ANP in the intermittent therapy group. Panel D: ANP at each sampling period in the intermittent therapy group. The numbers 8, 10, 12, and 16 on the X axis indicate 8 AM, 10 AM, noon, and 4 PM, respectively. Values are mean±SEM. **p<0.05 vs. day 4; ***p<0.05 vs. 8 AM on day 5; +++p<0.05 vs. 8 AM on day 5 and day 6.

therapy group, with complete reversal of heart rate and blood pressure responses within 26 hours of the onset of therapy. This was associated with increased levels of plasma norepinephrine, plasma renin activity, and arginine vasopressin along with retention of sodium, an increase in body weight, and a fall in hematocrit. Although plasma volume was not measured, it is likely that the retention of sodium was associated with both an increase in total body water and an increase in intravascular volume. The latter conclusion is supported by the greater decrease in hematocrit seen in the continuous than in the intermittent therapy group. Plasma volume expansion may also have occurred because of a redistribution of extravascular fluid to the intravascular space secondary to modification in Starling forces in the capillary bed caused by preferential dilation of venules as opposed to arterioles.14,19 The fact that atrial natriuretic peptide levels increased after the first day of therapy may well be a reflection of this intravascular volume expansion. Despite increased plasma renin activity, aldosterone levels were not significantly elevated in the continuous therapy group. This may reflect the small sample size and the fact that the increase in plasma renin activity was quite modest. In both groups, aldosterone levels actually became depressed by the third day of therapy. Although this may have been secondary to intravascular volume expansion in the continuous therapy group, it is difficult to invoke this explanation in the intermittent therapy group. Therefore, the cause of the decrease in plasma aldosterone in the intermittent therapy group remains uncertain. A possible explanation for this finding is that measurements of plasma levels are an incomplete description of hormonal activity; they do not reflect changes in receptor number or receptor responsiveness, and further, they do not accurately represent the activity of local hormonal systems within tissues.

It should be noted that some of the hormonal responses were transient, with plasma renin activity and arginine vasopressin returning to baseline levels by the third day of therapy. Because heart rate and blood pressure had also returned to pretreatment values at that time, it might be suggested that this provides evidence that the nitrates were no longer
Continuous Therapy

**Figure 5.** Arginine vasopressin (AVP) levels in ng/L on the day before nitroglycerin therapy (day 4) and on each of the treatment days (days 5–7). Panel A: Mean daily AVP in the continuous therapy group. Panel B: AVP at each sampling period in the continuous therapy group. Panel C: Mean daily AVP in the intermittent therapy group. Panel D: AVP at each sampling period in the intermittent therapy group. The numbers 8, 10, 12, and 16 on the X axis indicate 8 AM, 10 AM, noon, and 4 PM, respectively. Values are mean ± SEM. **p < 0.05 vs. day 4.

Exerting a physiological effect. This does not appear to be the case however, because there was substantial evidence of continued hormonal activity throughout the treatment period, as norepinephrine levels remained elevated, sodium retention persisted, and subjects continued to gain weight. All these findings suggest continued vascular effects of GTN, even though hemodynamic parameters had returned to baseline values.

Intermittent therapy with transdermal GTN was not associated with the development of tolerance. In contrast with the continuous therapy group, these subjects did not gain weight or exhibit sodium retention. Intermittent nitrate therapy was associated with significant increases in norepinephrine and plasma renin activity, but after the 12-hour nitrate-free interval, values consistently returned to pretreatment levels. In general, the response of arginine, vasopressin, and atrial natriuretic peptide was less marked during intermittent than during continuous therapy. Interestingly, there was a distinct increase in atrial natriuretic peptide levels after each 12-hour nitrate-free interval, a finding that was not anticipated and remains unexplained. Thus, intermittent GTN therapy was associated with a different pattern of neurohormonal response, and it appears that the nitrate-free interval allows for reversal of those counter-regulatory responses that occur during the treatment period. Although this may be part of the explanation as to why intermittent therapy is generally not associated with the development of tolerance, no definite conclusions regarding this point can be drawn from the present investigation.

Investigations in normal volunteers and patients with coronary artery disease have revealed increases in plasma catecholamines and activation of the renin-angiotensin system during short-term therapy with transdermal GTN. In one study, it was concluded that continuous nitrate therapy was not associated with sodium and water retention because the subjects did not gain weight during the treatment period. This was an outpatient study, without careful control of sodium and caloric intake, and thus firm conclusions regarding this point are difficult to make.

Neurohormonal activation in response to treatment with organic nitrates has been reported in some but not all studies in patients with congestive heart failure. Packer et al demonstrated that continuous therapy with intravenous GTN was asso-
ced with increases in plasma renin activity along with an increase in body weight. However, in other studies, there was no significant change in plasma renin activity or plasma catecholamine levels during therapy with GTN. Dupuis et al. found an increase in plasma renin activity during therapy with intravenous GTN in patients with congestive heart failure, although this was not associated with sodium and water retention. This investigation did document a rapid increase in intravascular volume after GTN therapy, a response that was felt to be secondary to a redistribution of extracellular fluid to the intravascular space. Thus, the nature of the counter-regulatory responses to nitrate therapy in congestive heart failure is not completely understood. It would not be surprising, however, if the responses were different from those seen in patients with normal hemodynamics, because patients with congestive heart failure have significant baseline differences in basal activity of many of these hormonal systems.

Although this study demonstrates that significant counter-regulatory responses occur during nitrate therapy, it is not possible to conclude that they are solely responsible for the attenuation in nitrate responsiveness seen with continuous therapy. There continues to be evidence that nitrate tolerance is due in part to a loss of the direct pharmacological vasodilating properties of these agents secondary to sulfhydryl group depletion at the level of vascular smooth muscle. The fact that the administration of the exogenous sulfhydryl group donor N-acetylcysteine is capable of partially reversing clinical tolerance to nitrates in patients with congestive heart failure, unstable angina, and coronary artery disease provides strong support for this hypothesis. This issue remains controversial, however, as some investigations have shown that sulfhydryl group donors are not effective in the reversal of tolerance and others have suggested that the effects of sulfhydryl group donors may be mediated through a tolerant-independent reaction between GTN and N-acetylcysteine in plasma.

Because many of the hemodynamic and symptomatic responses to nitrate therapy result from the potent preload reducing effects of these agents, we hypothesize that the counter-regulatory responses documented in this investigation play a role in the loss of effectiveness that is seen during continuous therapy with the organic nitrates. The release of a number of endogenous vasoconstrictors, retention of sodium, and the expansion of plasma volume would tend to reverse the preload reduction caused by nitrates, thus restoring intracardiac pressures toward normal. Importantly, these responses could effectively blunt the hemodynamic responses to nitrates even though the drug remained active at the cellular level. These counter-regulatory responses are likely to be important in the development of tolerance, and their modification through intermittent dosing intervals or some form of pharmacological intervention may allow continued nitrate responsiveness during sustained therapy.

It is possible that angiotensin converting enzyme inhibitors may prevent the development of nitrate tolerance either through their ability to act as sulfhydryl group donors (in the case of sulfhydryl group containing agents like captopril) or via their ability to block the effects of the renin-angiotensin system. Although the importance of these agents as sulfhydryl donors remains unclear, a recent investigation did demonstrate that concurrent therapy with a nonthiol angiotensin converting enzyme inhibitor was able to prevent the development of nitrate tolerance as assessed by forearm blood flow responses. The main finding of this investigation, that inhibition of the renin-angiotensin system is associated with continued nitrate responsiveness, lends strong support to the hypothesis that neurohormonal activation and plasma volume expansion contribute to the development of nitrate tolerance.

This investigation also suggests that diuretics may have a role in the prevention or modification of nitrate tolerance. Their effectiveness in preventing plasma volume increases during vasodilator therapy in hypertension is well established. Importantly, a recent preliminary report suggested that concurrent diuretic therapy prevented the development of tolerance to four-times-daily therapy with isosorbide dinitrate in patients with coronary artery disease.

Summary

Therapy with transdermal GTN is associated with a number of reflex counter-regulatory responses that cause the release of endogenous vasoconstrictors, the retention of sodium and are associated with evidence of plasma volume expansion. These responses, acting in concert, would tend to reverse the preload reducing effects of GTN and thus, may be partly responsible for the blunted hemodynamic responses observed over time. Although other mechanisms may well be involved in nitrate tolerance, it is likely that these counter-regulatory effects play an important role and their presence affords the possibility of devising new methods of preventing the development of tolerance to the hemodynamic and antianginal effects of the organic nitrates.

Acknowledgments

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Key Words • nitroglycerin • neurohormones • counter-regulatory
Counter-regulatory responses to continuous and intermittent therapy with nitroglycerin.
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