Dose-response relationships in clinical pharmacology
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THE DOSE-RESPONSE CURVE IN INDIRECTLY ACTING DRUGS

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The pharmacological effect of most drugs is assumed to be directly related to the plasma concentrations of the drug and to the dose administered (1). That is, the administration of a selected dose of a drug, after its absorption into the body, will generate plasma concentrations that once distributed will almost immediately reach the receptor site and elicit a measurable effect (figure 1, panel A). The changes in plasma concentrations function of time will be followed by changes in the pharmacological effect. In this case, the representation of the measured pharmacological response function of the dose or the plasma concentrations will show the classical sigmoidal dose-response curve or the hyperbolic curve (figure 2). When the range of doses or concentra-

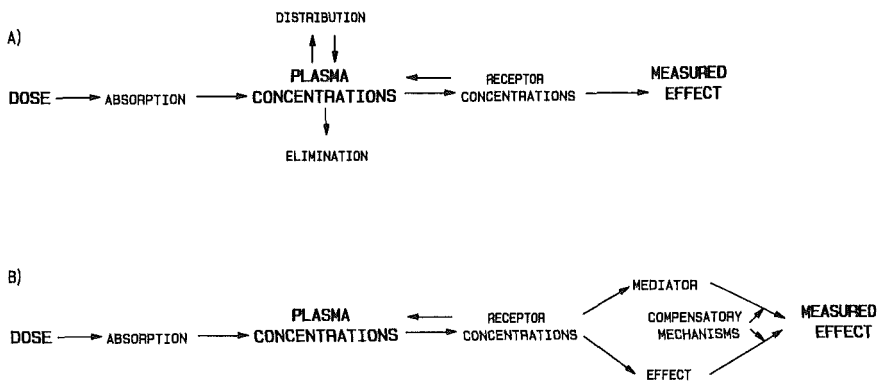

Fig. 1. Relationship between the administered dose, plasma concentrations and the measured pharmacological effect. Panel A represents a direct relationship between plasma concentrations and measured effect and panel B represents an indirect relationship.

tions studied is limited, a linear relationship between the pharmacological response and the dose or plasma concentrations may be observed. The presence of a direct dose-response relationship presumes that:

a) any change in the drug's plasma concentrations is rapidly followed by changes in the pharmacological effect, that is, the changes in the effect are not delayed,

b) the pharmacological effect does not activate counteracting reflex or compensatory mechanisms, and

c) the effect is directly related to the parent compound and not to the combined action of parent and active metabolites or the latter alone.

Theoretically, it is conceivable that the access of the drug to the receptor site may be slow, because the receptor is located in a remote anatomical situation. In such case, the delay observed between changes in plasma concentrations and pharmacological response will obscure the relationship between effect and plasma concentrations of the drug. The formation of active metabolites, when the metabolite to parent compound ratio increases with time, will also be responsible for a longer than expected response on the basis of the

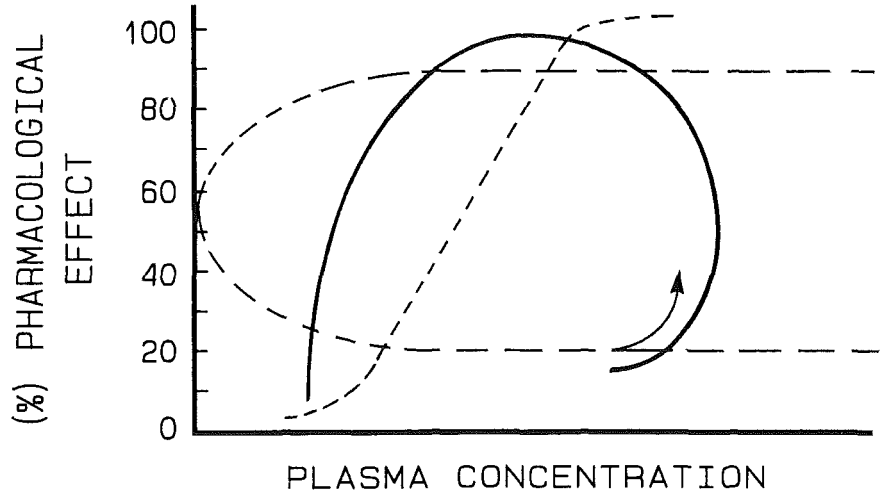

Fig. 2. Relationship between pharmacological effect and plasma concentrations of the drug. The sigmoidal and hyperbolic curves are the result of a direct relationship and the anticlockwise hysteresis loop is the result of a delayed or indirect relationship.

decay of the plasma concentrations of the parent compound. Many drugs will elicit an effect that will entail the activation of compensatory mechanisms,in such a way, that the measured pharmacological response will be the net effect result of the drug's response and the counteracting effect (figure 1, panel B); as a consequence, the changes in plasma concentrations will not parallel those of the pharmacological effect. In theory, any drug affecting the cardiovascular system, the hemodynamics or the endocrine system may activate compensatory mechanisms. In other cases, the net effect is regulated by the availability of a substrate, for example the effect of anticoagulants will depend on the balance between the concentrations of the drug and the rate of formation of the clotting factors; many toxic effects depend upon the concentration of the toxicant and the availability of detoxification substrates. On the other hand, other drugs will not exert their effect directly but rather, by activating a mediator that will elicit the measured effect. Under most of these circumstances, the measured response will be delayed by reference to the changes in the plasma concentrations of the parent compound.

Occasionally, drugs eliciting an effect that results from complex interactions, will still show a direct relationship between the measured effect and plasma concentrations, as is the case with timolol (2) and theophylline (2). In many other instances, the graphic representation of the pharmacological response function of the plasma concentrations of a drug, with any of the characteristics listed above, may not show a direct relationship, but instead, an anticlockwise hysteresis loop (figure 2). Under such circumstances, it is almost impossible to determine the properties of the effect-concentration relationship. In order to eliminate the anticlockwise hysteresis it will be necessary to plot the effect function of the concentrations of the drug estimated in other compartments; for instance, Galeazzi et al. (3) observed that when the increment in the corrected QT interval was plotted against procainamide plasma concentrations, an anticlockwise hysteresis loop was depicted, however, the hysteresis was eliminated when the increment in the correted QT interval was plotted against the predicted procainamide concentrations in saliva. In our laboratory, we have observed that in cirrhotic patients, the increase in natriuresis and diuresis was not associated with furosemide plasma concentrations, however, a direct (hyperbolic) relationship was obtained when the effect was plotted against furosemide urinary excretion rate (unpublished results).

When the anticlockwise hysteresis loop results from the presence of regulatory mechanisms, the relative importance of these counter-regulatory mechanisms may be overcame by changes in the dosage of the drug. The

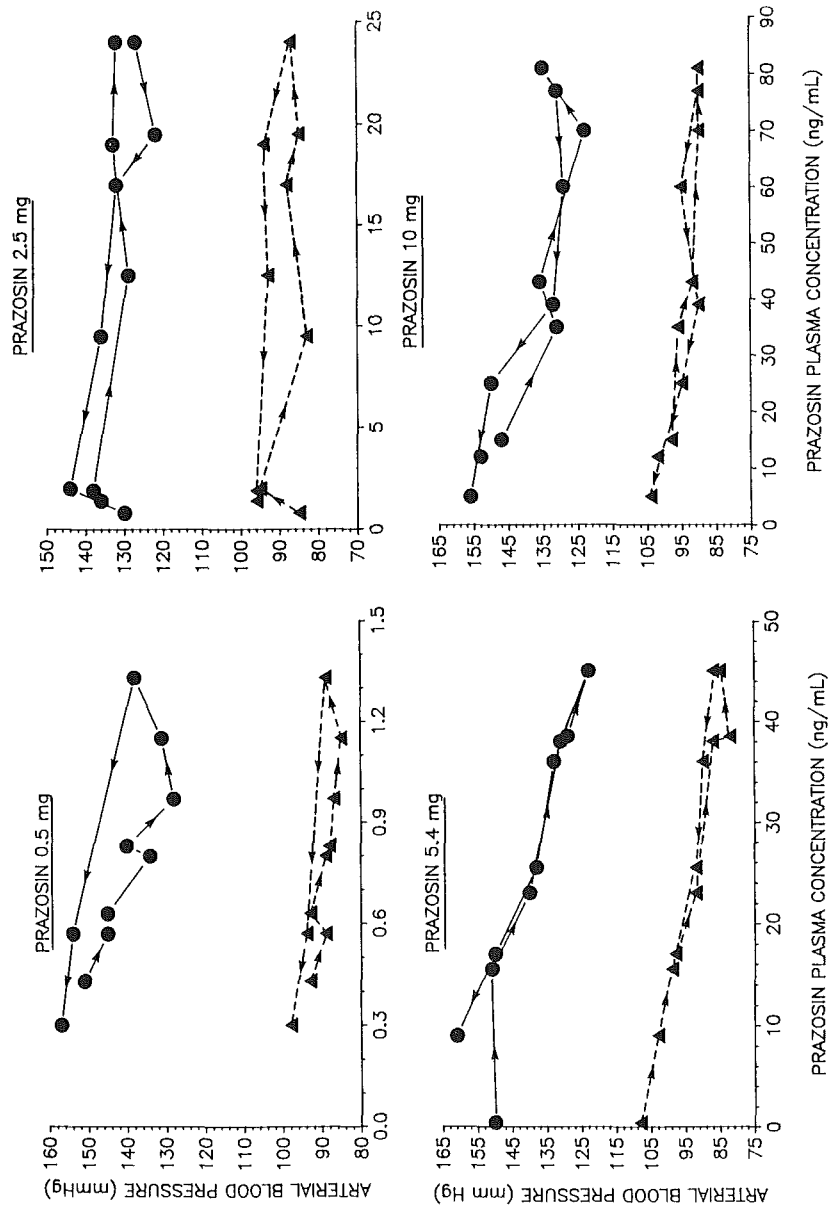

Fig.3.Changes in arterial blood pressure (o--o systolic and ····· diastolic) function of prazosin plasma concentrations. The anticlockwise hysteresis loop observed with the 0.5 and 2.5 mg doses was eliminated with higher doses of prazosin (5.4 or 10 mg).

hypotensive effect of several doses of prazosin (0.5, 2.5, 5,4 and 10 mg), administered to 16 subjects with essential hypertension (4), has been plotted against prazosin plasma concentrations; as shown in figure 3, the effect of low doses of prazosin plotted against prazosin plasma concentrations depicted an anticlockwise loop, which was progressively eliminated as the doses were increased.

In other instances, to define the properties of an effect function of the drug's concentration it will be necessary to estimate the concentrations of the drug at the effect-site. However, since most times the values of the concentrations of the drug at the receptor site are unknown, it will be necessary to estimate them using the approach proposed by Forrester et al. (5). When the drug reaches and leaves the effect site by a first order process, the time course of drug accumulation at the effect site can be predicted using the model shown in figure 4. Details concerning the model and equations describing this kinetic model have been extensively discussed by

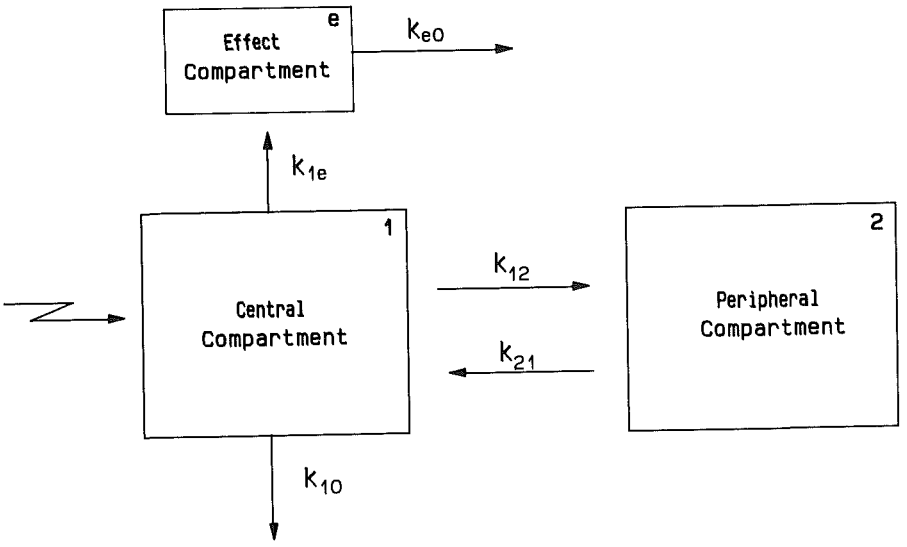

Fig. 4. Pharmacokinetic model of a drug eliciting its pharmacological effect in a peripheral or effect compartment.

Holford and Sheiner (2,6,7). Among others, this approach has been successfully used to describe the effect of d-tubocurarine (8), the hypokaliemic effect of terbutaline (9) and the prolactin suppressant effect of a dopaminergic agonist (10).

We report here the integrated pharmacokinetic-pharmacodynamic model describing the pharmacological effect of atrial natriuretic factor (ANP), administered as a bolus injection or as an infusion. ANP appears to elicit two main effects: an increased natriuresis and diuresis and a hypotension by acting on the kidney and on the cardiovascular system. ANP effects are not generated from the direct interaction ANP-receptor site but probably, mediated by cyclic guanosine monophosphate (cGMP). As a consequence, the changes in effect function of time are delayed compared with the changes in ANP plasma concentrations function of time.

BOLUS INJECTION OF ATRIAL NATRIURETIC PEPTIDE

Six healthy subjects received a rapid injection of ANP, three of them 50 mcg and three 100 mcg. Multiple blood samples were withdrawn to assay ANP, cGMP,

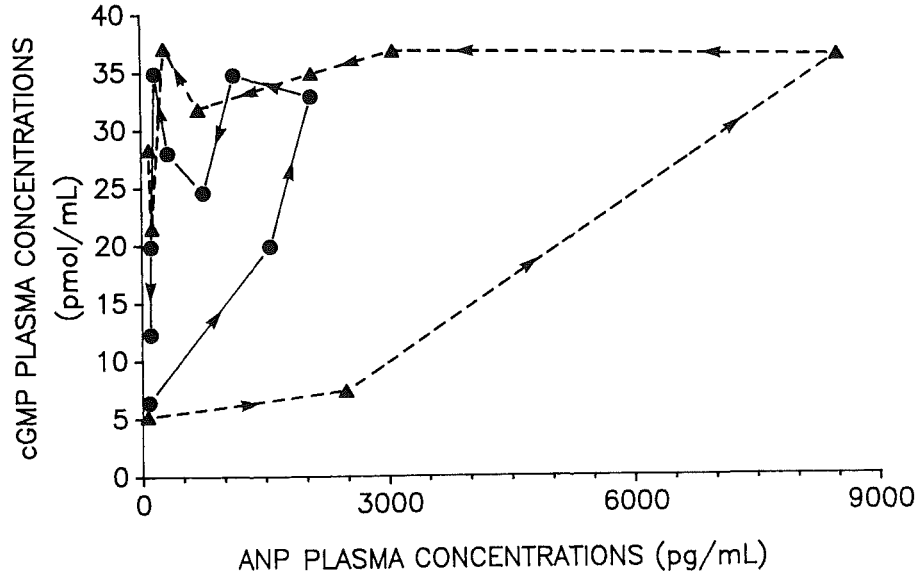

Fig. 5. Changes in plasma cGMP concentrations funtion of ANP plasma concentrations, following the intravenous administration of 50 or 100 mcg of ANP.

Na^+, K^+, plasma renin activity (PRA), aldosterone, arginine vasopressin (AVP), dopamine, epinephrine and norepinephrine. Urine was collected at 1 hour intervals to measure the diuresis, Na^+ and K^+. Blood pressure and cardiac rate was measured at 1 minute intervals. The details of the experimentalprotocol have been published elsewhere (11).

Following the injection of 50 or 100 mcg of ANP, baseline ANP plasma concentrations increased from 80 ± 4 to 2071 ± 279 pg/mL or from 61 ± 1 to 8514 ± 534 pg/mL, respectively. Thirty minutes later, ANP plasma concentration values had returned close to baseline levels. Mean plasma cGMP peaked at 5 (34.8 ± 6.2 pmol/mL) or at 15 minutes (37.1 ± 3.8 pmol/mL) for the 50 and 100 mcg doses, respectively, and 60 minutes later, these concentrations were still higher than baseline values. Neither natriuresis nor diuresis increased significantly after the administration of the 50 mcg dose of ANP, while blood pressure showed a tendency to decrease. However, following the administration of the 100 mcg dose, diuresis increased from a mean baseline rate of 1.62 to 1.35, 1.79, 3.25 and 4.33 mL/min at 1, 2, 3 and 4 hours; mean baseline excretion rate of sodium was 129, and increased to 138, 172, 238 and 278 µmol/min at 1, 2, 3 and 4 hours. Blood pressure, both systolic and diastolic, decreased rapidly and transiently by approximately 8 mmHg after the administration of ANP.

The decay of ANP plasma concentrations function of time, on a semilogarithmic scale, depicted two well defined phase, therefore, it was considered that ANP confered to the body the characteristics of a two compartment model. cGMP plasma concentrations were plotted against ANP plasma concentrations, assuming that the changes in cGMP are caused by ANP. The resulting plot depicted an anticlockwise hysteresis loop, and that for both ANP doses (figure 5), suggesting that the stimulation of cGMP synthesis by ANP is a delayed effect. This figure also shows that the effect obtained with ANP plasma concentrations of 8514 pg/mL is not superior to the one obtained with plasma concentrations of 2071 pg/mL, suggesting that cGMP stimulation is a saturable process.

To eliminate the hysteresis we assumed that the effect of ANP, e.g. stimulation of cGMP, does not occur in the central compartment, but rather in a peripheral one (figure 4). To predict ANP plasma concentrations in this compartment effect, the effect data were fitted to an integrated model using an equation describing the kinetics of ANP in the compartment effect (C_{ef}) and a pharmacodynamic model describing the time course of drug effect (E) (6):

$$C_{ef}=\frac{D\cdot ke0}{V}\left[\frac{(k21-\alpha)\cdot e^{-\alpha\cdot t}}{(\beta-\alpha)(ke0-\alpha)}+\frac{(k21-\beta)\cdot e^{-\beta\cdot t}}{(\alpha-\beta)(ke0-\beta)}+\frac{(k21-ke0)\cdot e^{-ke0\cdot t}}{(\alpha-ke0)(\beta-ke0)}\right] \qquad (1)$$

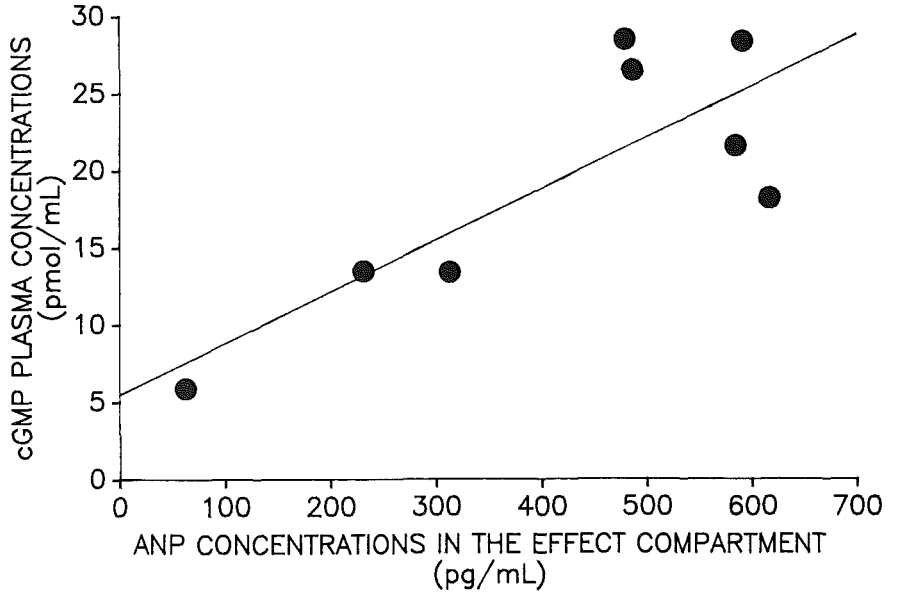

Fig. 6. Changes in plasma cGMP concentrations funtion of predicted ANP concentrations in the effect compartment, following the intravenous administration of 50 mcg of ANP.

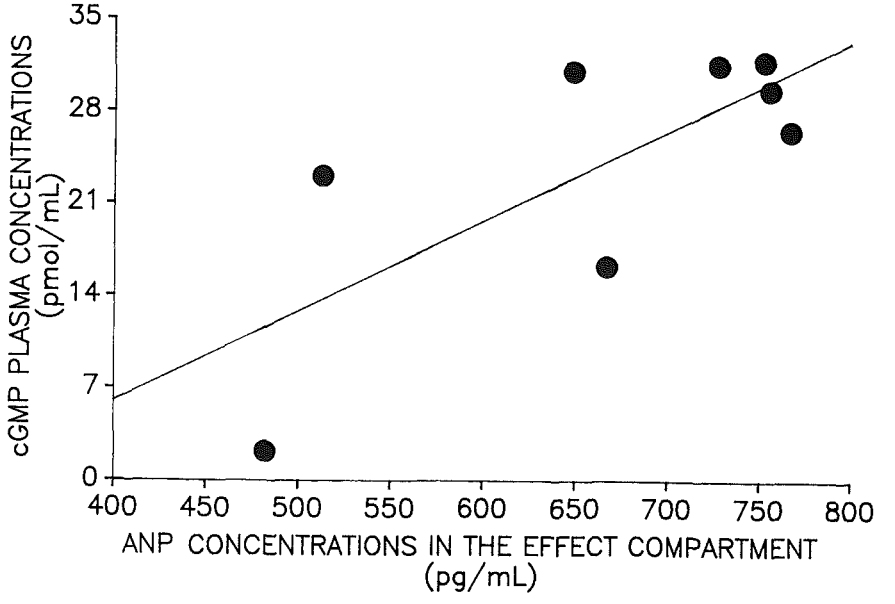

Fig. 7. Changes in plasma cGMP concentrations funtion of predicted ANP concentrations in the effect compartment, following the intravenous administration of 100 mcg of ANP.

$$E = E_B \pm \frac{Emax \cdot C_{ef}^{\,n}}{EC_{50} + C_{ef}^{n}} \qquad (2)$$

Where keO is the equilibration rate constant, E_B and Emax are the baseline and maximum effect, respectively, and EC_{50} is the concentration of ANP required to produce 50% of Emax. The value of the remaining parameters was estimated from ANP plasma concentrations fitting, using a nonlinear regression curve fitting computer program (PC-NONLIN).

As shown in figures 6 and 7, plasma concentrations of cGMP plotted against predicted ANP concentrations in the compartment effect almost completely eliminated the hysteresis. The direct relationship between cGMP and ANP now becomes much more evident, specially following the 50 mcg dose. From the analysis of the cGMP-ANP relationship, several conclusions can be drawn:

a) the predicted maximum ANP concentration in the effect compartment, after the 50 mcg dose, is similar to the concentration observed after the 100 mcg dose, e.g. 617 v.s. 767 pg/mL respectively,

b) the predicted maximum cGMP concentration (Emax) appears to be independent of ANP dose and is of the order of 40 pmol/mL, suggesting that cGMP formation is a saturable process,

c) the ANP concentration in the effect compartment that elicits 50% of Emax is of the order of 500 pg/mL, and

d) the equilibration rate constant (keO) is, in average, 0.0556 and 0.0088 min^{-1}, for the 50 and 100 mcg doses respectively,

In theory, these results explain why both ANP doses produce a similar effect on cGMP, e.g. maximum ANP concentrations in the effect compartment were almost identical. However, the model used can not distinguish between a saturable access of ANP to the effect compartment, a limited number of receptors, and from a saturation of cGMP formation, therefore, the exact mechanism can not be determined. On the other hand, the predicted half life of ANP in the compartment effect differed significantly between doses, e.g. 13 and 79 minutes, indicating that ANP plasma concentrations in the compartment effect should be close to zero after one and seven hours following the 50 and 100 mcg doses, respectively. By extension, if the measured effect of ANP on the kidney and on the blood pressure are dependent on the increase in cGMP, it is possible to predict that these effects should vanish in one or in seven hours, depending on the dose administered. We have no explanation on why after the 50 mcg dose no effect was detected even with elevated cGMP plasma levels; we may speculate that at the 50 mcg dose, the compensatory mechanisms (other than the ones measured in this study) efficiently masked the effect of ANP, or that cGMP

is not mediating the measured effects of ANP, or alternatively, that the effects were of too small and of short duration to be properly evaluated.

The relationship between diastolic or mean blood pressure and ANP plasma concentrations, following the 100 mcg dosage, was adequately described by the pharmacodynamic Emax model (equation 2). On the other hand, the diuretic and natriuretic effect of ANP could not be associated neither with ANP plasma concentrations nor with the predicted ANP effect compartment concentrations. These results suggest that despite both doses elicited a similar effect on cGMP, the final effect on blood pressure or kidney function differed between doses.

It is obvious from these results, that following the rapid intravenous administration of ANP to healthy volunteers, the relationship ANP-cGMP-effect is obscure. Several hypothesis could be postulated: firstly, the response to an intravenous injection of ANP is related to the increase in cGMP, but ANP or cGMP kinetics are zero-order; secondly, the effect of ANP on blood pressure and on the kidney are independent of cGMP, and thirdly, the measured effects (blood pressure, natriuresis and diuresis) result from the direct effect of cGMP but partially counteregulated by other systems, dependent upon the dose of ANP, since the intensity and kind of counter-regulatory mechanism may be associated to the dose of ANP.

INFUSION OF ATRIAL NATRIURETIC PEPTIDE

Seven healthy subjects with a mean age of 28 years and 5 patients with mild essential hypertension and a mean age of 32 years were included in the study. All patients had a diastolic blood pressure greater than 100 mmHg but without target-organ damage; none of the patients was taking any medication. The subjects were given a daily diet with 150 mmol of Na^+ and 100 mmol of K^+, and, on day 6, an infusion of ANP at three consecutive rates of 0.8, 1.6 and 3.2 µg/min for 30 minutes. Blood samples were withdrawn to assay ANP, cGMP, Na^+, K^+, AVP, catecholamines, aldosterone, PRA and dopamine. Urine was collected to measure the diuresis, Na^+ and K^+. Blood pressure and cardiac rate were measured at 1 minute intervals. The details of the experimental protocol are published elsewhere (12).

In control subjects, at the end of the three infusions, plasma ANP concentrations were 58 $\pm$ 7, 177 $\pm$ 30 and 232 $\pm$ 35 pg/mL and in patients with hypertension, 68 $\pm$ 11, 179 $\pm$ 39 and 233 $\pm$ 50 pg/mL at 30, 60 and 90 minutes, respectively. Visual inspection of ANP plasma levels suggested that the steady state was attained at the three rates of infusion. The decay of plasma ANP showed a single phase, suggesting that ANP confered to the body the characteristics of a single compartment model. Plasma cGMP concentrations,

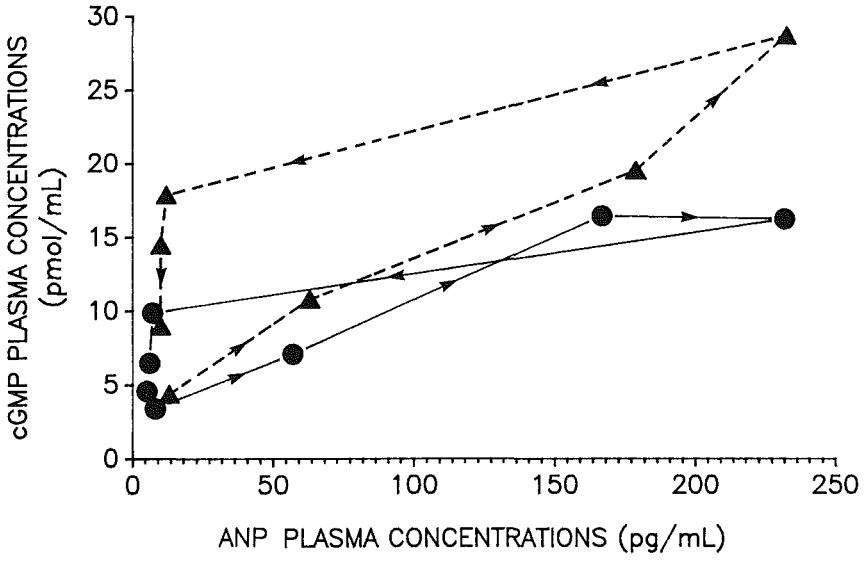

Fig. 8. Changes in plasma cGMP concentrations function of ANP plasma concentrations, following the infusion of ANP to healthy (o—o) and hypertensive patients (···).

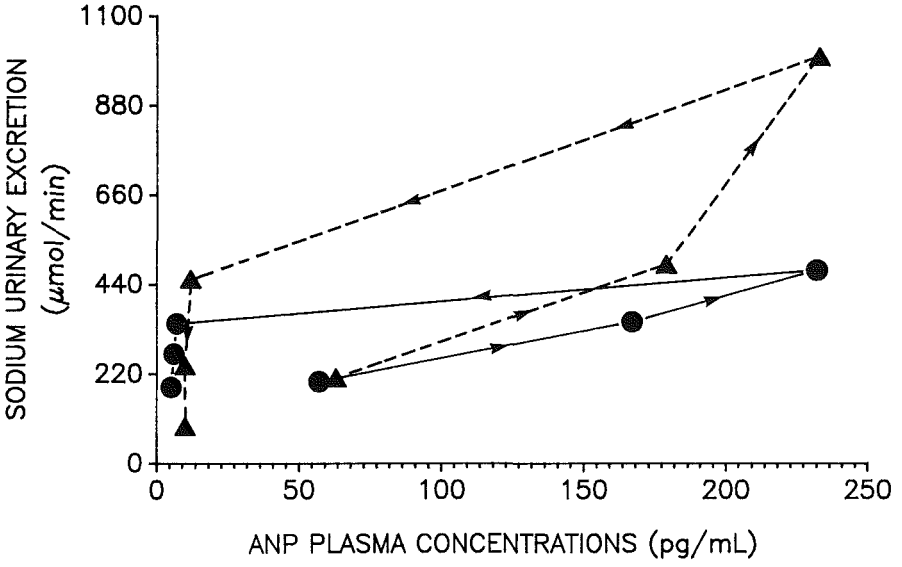

Fig. 9. Changes in sodium urinary excretion function of ANP plasma concentrations following the infusion of ANP to healthy (o—o) and hypertensive patients (···).

sodium urinary excretion and diuresis increased in control and in hypertensive patients during the first 30 minutes of ANP infusion, to reach a peak at 90 minutes and thereafter, to return to baseline levels by 180 minutes.

Assuming that the changes in cGMP plasma concentrations, sodium urinary excretion and diuresis are originated by the administration of ANP, plotting the value of the changes in these parameters against ANP plasma concentrations should depict a dose-response curve; instead, the resulting plot showed an anticlockwise hysteresis loop and that, for normal and for hypertensive subjects (figure 8 to 10). Interestingly, the stimulation of cGMP, natriuresis and diuresis was significantly superior in hypertensive subjects, even if ANP steady state plasma levels and ANP kinetics were identical, e.g. 232 and 233 pg/mL at 90 minutes, systemic clearance of 13.8 and 13.7 L/min and volume of distribution of 99 and 83 L, for control and patients respectively.

To eliminate the hysteresis we assumed that ANP effect, e.g. the increase in cGMP, in sodium urinary excretion and in diuresis, occurs in a compartment other than the central compartment, a peripheral compartment. To estimate the plasma concentrations of ANP in this compartment effect, the effect data were fitted to an integrated model using an equation describing the kinetics of ANP in the compartment effect (C_{ef}) following its infusion (equation 3) and a pharmacodynamic model describing the time course of drug effect (equation 2) (6).

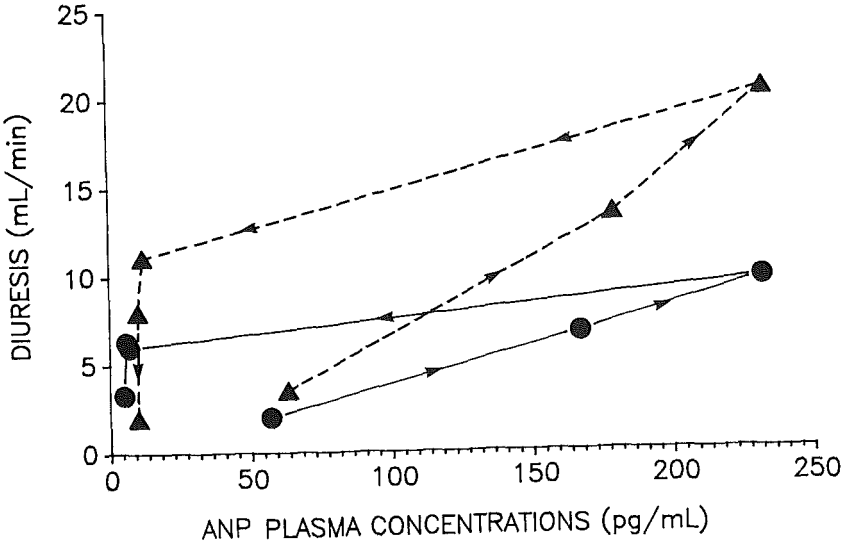

Fig. 10. Changes in diuresis funtion of ANP plasma concentrations following the infusion of ANP to healthy (o—o) and hypertensive patients (····).

$$C_{ef} = \frac{ko \cdot keO}{V} \left[\frac{(e^{kel.TI} - 1) \cdot e^{-kel.t}}{kel \cdot (keO - kel)} + \frac{(e^{keO.TI} - 1) \cdot e^{-keO.t}}{keO \cdot (kel - keO)} \right] \quad (3)$$

Where ko is the rate of ANP infusion, kel the rate constant of ANP elimination from the central compartment and TI the time of infusion. As shown in figure 11, plasma concentrations of cGMP plotted against the predicted ANP concentrations in the effect compartment eliminated the hysteresis, for normal volunteers as well as for patients with hypertension. However, the characteristics of this effect in healthy volunteers differed substantially from the ones in hypertensive patients: the keO was 0.9110 and 0.0763 min^{-1}, the Emax was 54 and 76 pmol/mL and the CE50 was 42 and 78 pg/mL, respectively. The predicted characteristics of ANP effect suggest that in hypertensive patients the maximum effect is higher and the duration of this effect is longer than in healthy subjects. Interestingly, urinary sodium excretion and diuresis were directly associated with ANP concentrations in the effect compartment, but only for hypertensive patients.

To try to understand the differences in the response to ANP it is important

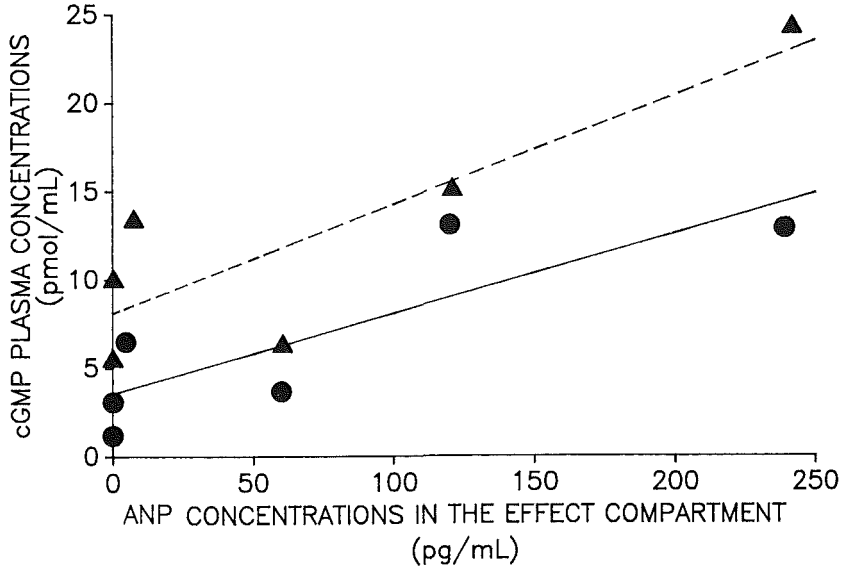

Fig. 11. Relationship between cGMP plasma concentrations and predicted ANP concentrations in the effect compartment, in normal volunteers (o—o, r^2= 0.7041,p<0.05) and hypertensive patients (▲···▲, r^2= 0.7252, p<0.05).

to remember its effects. The combining effects of ANP on systemic and renal hemodynamics and on renal water and sodium excretion suggest that ANP has a role in the regulation of arterial pressure. Administration of pharmacological doses of ANP resulted in a sustained fall in arterial pressure, mainly due to a decrease in venous return and cardiac output. ANP posseses potent vasodilating properties on vascular preparations, apparently associated with an increased production of cGMP. ANP also opposes the vasoconstrictor effects of several agonists, such as cathecholamines, angiotensin II and AVP, effect that may contribute to reduce the systemic vascular resistances, particularly under stimulated conditions. ANP also interferes with the sodium retaining properties of aldosterone, both directly and indirectly, by inhibiting its production and possibly by reducing angiotensin II, which results from the inhibition of renin secretion. In addition, ANP appears to suppress the central pressor effect of angiotensin II and the liberation of AVP. On the kidney, it seems that both renal hemodynamic and tubular actions of ANP contribute to the excretion of a hypernatric urine. ANP effect on the natriuresis and diuresis is, at least in part, independent of its effect on blood pressure, but also appears to be mediated by cGMP (13). The net effect of ANP depends on the baseline situation and the counter-regulation mechanisms stimulated by ANP effect on the blood pressure

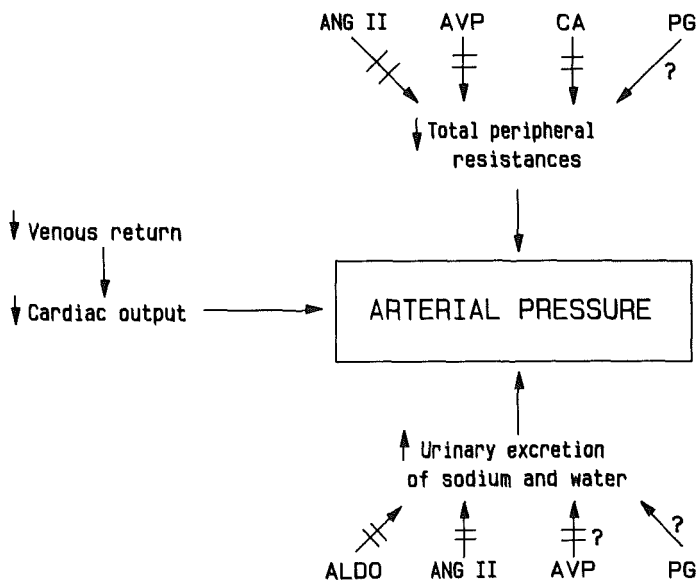

Fig. 12. Effect of ANP on total peripheral resistances, cardiac output and urinary excretion of sodium and water, and its repercussions on blood pressure. indicates a decrease in its plasma concentrations and an increase.

and by the dose of ANP (figure 12).

In conscious subjects, on a normal sodium diet, hypotension will activate the systems eliciting a vasoconstriction, as well as those forcing the kidney to retain sodium, resulting in an increase in cardiac output. However, in healthy volunteers, after a 50 or 100 mcg dose of ANP, none of the counter-regulatory markers measured (PRA, catecholamines, aldosterone and dopamine) were enhanced; only plasma concentrations of AVP decreased significantly from 4.4 $\pm$ 0.1 to 2.6 $\pm$ 0.4 pg/mL. Following the infusion of ANP, despite that 4 subjects experienced sudden weakness, nausea and pallor and a decrease in blood pressure, the values of PRA decreased but none of the other parameters were affected. In patients with hypertension, the infusion of ANP did not affect blood pressure nor PRA, AVP, aldosterone, epinephrine or dopamine, but increased norepinephrine plasma concentrations, as well as did heart rate. It must be remembered that these parameters were estimated only at the end of the infusion.

The hypotensive response to ANP does not appear to parallel its natriuretic effect. Following the bolus, high levels of ANP (increasing baseline levels 140 fold) produced an almost immediate decrease in blood pressure but delayed changes in renal function. On the other hand, the infusion of ANP (increasing

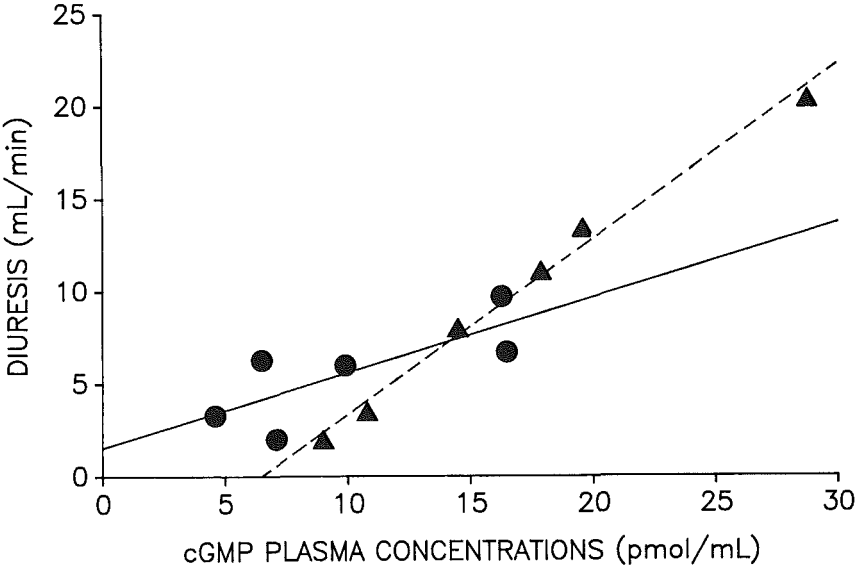

Fig. 13. Relationship between diuresis and cGMP plasma concentrations in normal volunteers (-o-, r^2= 0.6724, $p<0.05$) and hypertensive patients (···, r^2= 0.9900, $p<0.001$).

baseline levels 30 fold) exerted a marked effect on renal function and only a transient effect on blood pressure. These results suggest that time of exposure, rather than level of ANP attained, is important for the renal response, at least in absence of detectable counter-regulatory mechanisms. Furthermore, our results suggest that cGMP does not mediate ANP hypotensive effect but may mediate ANP renal effects; effectively, changes in blood pressure were associated to ANP plasma concentrations suggesting a direct relationship, and on the other hand, cGMP, natriuresis and diuresis plotted against ANP plasma concentrations depicted an anticlockwise hysteresis loop, which was eliminated when cGMP was plotted against predicted ANP concentrations in the effect compartment. This hypothesis is further supported by the fact that urinary excretion of sodium as well as the diuresis were directly related to cGMP concentrations, and that for normal subjects and for hypertensive patients (figures 13 and 14).

It is interesting to note that the predicted maximum increase in cGMP appears to be independent of the dose or way of ANP administration or of the presence of hypertension, since similar values of Emax were estimated under all circumstances tested. However, the predicted values for ANP concentration

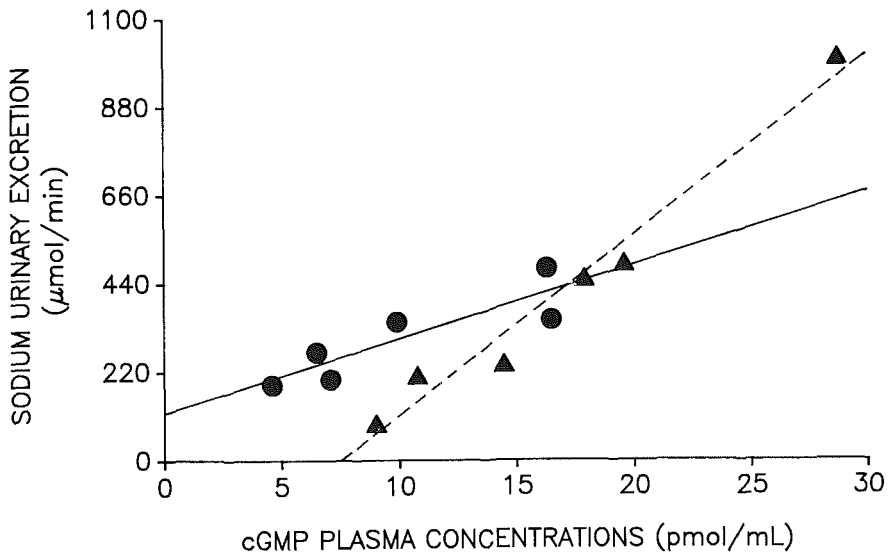

Fig. 14. Relationship between sodium urinary excretion and cGMP plasma concentrations in normal volunteers (-o-, r^2= 0.7586, $p<0.05$) and hypertensive patients (···, r^2= 0.9722, $p<0.001$).

(CE_{50}) that elicited 50% the Emax differed substantially among the subjects and ways of administration: 42 and 78 pg/mL for normal and hypertensive patients being infused with ANP, and 500 pg/mL for the 50 and 100 mcg bolus to normal volunteers. Being ANP rate constant of elimination of 0.2529 min^{-1} and the rate of distribution of 0.3046 min^{-1}, we may postulate that the observed differences between the bolus and the infusion reflect in fact the poor accessibility of ANP, with a m.w. of around 3000 daltons, to the receptor site; that is, due to ANP rapid elimination, after a bolus only a small amount of peptide reach the receptors. That may not be the case when the peptide is infused.

With the present data it is difficult to explain why hypertensive subjects elicit a much greater response to identical plasma concentrations of ANP than do healthy subjects. This difference is probably associated with factors related to the characteristics of the homeostasis of sodium and water in hypertension.

Assuming that the measure of the counter-regulatory markers at the end of the infusion reflects the levels maintained all along the infusion, we can conclude that, independently of the way of administration, ANP induced minimal compensatory mechanisms. Bearing this in mind, we may propose that the mechanisms originating the indirect response to ANP are:

a) the ANP-induced stimulation of cGMP, because of the multiple steps involved or a saturation of cGMP formation,

b) the way of administration of ANP,

c) the underlying pathology, and

d) to a minor degree, the counter-regulatory mechanisms.

The present study demonstrates that an indirect effect can be characterized using a rather simple integrated pharmacokinetic-pharmacodynamic approach. Indeed, the data generated may have physiological or pharmacological relevance whenever the intermediate steps are limited and can be properly defined. Other- wise, the characteristics of the effect-concentration relationship will only reflect a summary of the events occurring between the plasma concentrations and the measured effect.

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Discussion - The dose-response curve in indirectly-acting drugs

D.G. Grahame-Smith

Cyclic GMP is an intracellular mediator and leaks out in a rather undefined way into the plasma. It is very interesting that you get a dose respose relationship between the level of ANP and cyclic GMP, but don't you find it rather surprising that you do, considering all the cascade of events that would have to occur?

B.P. du Souich

There was no correlation between cyclic GMP and ANP plasma concentrations. What we found was that cyclic GMP plasma levels were related to the estimated ANP concentration in the effect compartment. Actually, it is interesting to notice that cGMP plasma concentrations did directly correlate with the diuretic response to ANP.

R.L. Galeazzi

You were the first today to introduce a mathematical model to describe the dose-effect relationship in humans, the E_{max} model, and I wonder why don't we have more data and more analysis in this way? I would like to teach it to the practitioners or to the students. 50 years ago, the concept of drug half life was introduced and today everybody knows about it. It might not be the best pharmacokinetic parameter, but one can work with it. Why don't we have some concept in effect kinetics that is like the half life?

B.P. du Souich

As you are well aware, the kinetics of drug effects were described many years ago by Gerhard Levy. One can easily calculate the rate of disappearance of an effect and talk about a half life, but the problem is that the half life of the effect is not linear and increases with the dose. If the range of doses considered is rather narrow, the concept of half life of effects may be useful in the way that you suggest but otherwise it may be misleading. On the other hand, let me recognize that the use of the E_{max} model is not simple. It requires the use of a very wide dose range and the ability to saturate.

R.J. Temple

It is certainly interesting to see that one is able to use models in complicated situations like those created by indirect effects. However, I feel that even with simple drugs with direct effects much is still to be done in the way of applying the existing knowledge to clinical situations. In many cases we do not really know whether the area under the curve or the C_{max} or the C_{min} is really most important, because this information has not been developed.

E.A. Carr

I would like to mention a factor that in many instances precludes application of pharmacokinetic principles to a clinical situation and it is that information about the exact time of drug administration is awfully difficult to get in a ward. It is a very simple missing ingredient that tends to discourage people from using, under the practical situations of the clinic, a lot of information that they could otherwise use.