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Preliminary Results of Simulations with an Improved Mathematical Model of Drug Tolerance

In this preliminary report, results of simulations are described, performed with an improved version of a mathematical model published previously (Peper *et al.*; 1987, 1988). The present paper briefly describes the build-up of the model and its behaviour to different stimuli while some surprising results of simulations of different ways of withdrawal in addiction are presented. The significance of the model predictions for the development of optimal protocols for drug withdrawal will be investigated in a clinical project. On the basis of the effect of the different withdrawal schemes on addicted subjects, the model parameters will be optimized. A thorough and detailed description of the improved model and its behaviour to different stimuli is in preparation.

The model provides a general model of drug tolerance, drug dependence and drug addiction. The concept underlying the model establishes a relation between the - rapid - action of drugs and the slow build-up of tolerance: the defence of the organism to recurring disturbances of its functioning. The objective has been to elucidate the relations existing between the cellular mechanisms of drug tolerance, known from the literature, and processes in the organism above the cellular level participating in the tolerance process, in which the central nervous system is an important factor (Steffens 1976; Loewy & Haxhiu 1993). The model makes use of memory to account for the slow build-up of tolerance during successive administrations of a drug: the carry-over effect (Jaffe & Sharpless 1968). This slow adaptation of the organism to the effect of a drug implies that it is able to recognize a drug at the moment it is administered, before it exerts its effect upon the organism (Grill *et. al*. 1984). In previous publications (Peper *et al.*; 1987, 1988), we demonstrated that the mechanism responsible for the suppression of the drug effect after tolerance has developed, also is the cause of the reaction of the organism when the drug effect has ceased - the rebound mechanism - (Jaffe & Sharpless 1968; Seevers & Deneau 1968; Kalant *et. al*. 1971; Snyder 1977) and of the large reactions following the withdrawal of a drug after addiction has developed (Seevers 1968). These large reactions and the rebound effect are adequately described by the model as well as the involvement of the central nervous system and the psychological factor - anticipation of drug intake - which plays a major part in evoking the large reactions in addicted subjects.

Since the first publications of the mathematical model of drug tolerance, the model has been greatly improved. The present model accurately describes how changes of the level of a drug in the blood affect the behaviour of the different processes involved in the drug effect.

Model and Model Behaviour.

Fig. 1 shows a scheme of one of the possible configurations of the model. It depicts a certain process of which the output is regulated at a level set by the process reference. A messenger substance in the blood stream transmits information about the output level of the process to the process regulator. The concentration of the messenger substance is measured with a sensor: receptors with affinity to the messenger substance. The binding of messenger molecules

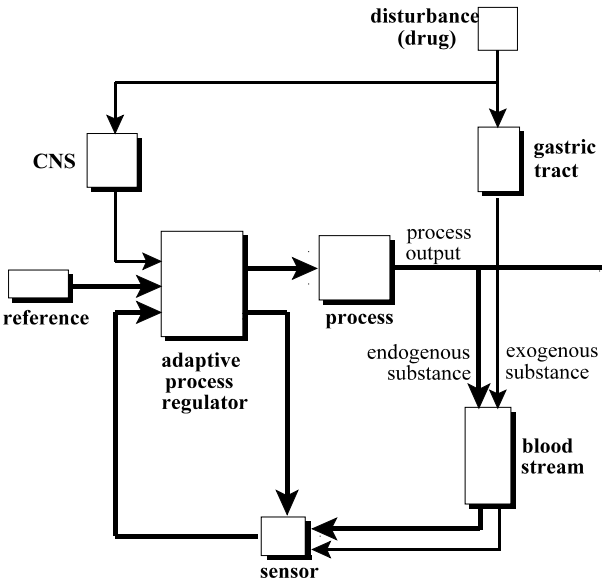

FIG. 1. Block scheme of the model.

with receptors results in a signal from the sensor to the process regulator with a magnitude which is a measure of the number of messenger molecules bound to the receptors and consequently a measure of the amount of the substance in the blood stream. The process regulator - the central part of the model - tries to minimize the difference between the sensor output and the reference level: it keeps the process at the desired level by negative feedback. Regulated processes in the organism can be disturbed in many different ways. A drug may change the level of a regulated substance in the organism by increasing it by its presence, when it is equal or related to the substance in question, or decreasing it, for instance by neutralization. The disturbing effect may also be caused by a change of the information transfer in the organism when, for instance, a drug causes a change of the number of receptors able to bind to a messenger substance. The process of development of tolerance by the organism to these different kinds of disturbances of regulated processes is fundamentally the same and can, in different configurations, all be simulated by the model. In the model shown in Fig. 1, the disturbance is caused by a drug which mimics the action of the messenger substance at the receptor site, increasing the output signal of the sensor. The agonistic action of the drug will cause the process regulator to decrease the process output to keep the sensor output equal to the reference level. The increase of the sensor output is the initial effect of the drug, or broadly generalizing, the drug effect. When instead of an agonistic drug an antagonist is administered, the drug effect is similar, but opposite.

The process regulator in the model describes the adaptive behaviour of the organism to a repeatedly occurring disturbance. It differs fundamentally from a process regulator of a process which is regulated by negative feedback only. When a drug is administered repeatedly, the adaptive process regulator gradually learns to suppress the effect of the drug. This learning process in general makes use of memory for very different aspects of the disturbance: memory for the properties of the particular drug, memory for the effects the drug had previous times it was present and memory for the measures which have to be taken to reduce the effect of the drug. The adaptive regulator suppresses the effect of a drug mainly during the time the drug is active. In the interval between drug taking its influence is relatively small, depending on the length of the interval. Its ability to suppress the drug effect slowly declines when the drug is withdrawn. The adaptive regulator accomplishes the suppression of the effect of a drug by changing the sensitivity of the sensor during the presence of the drug, for instance by changing the number of receptors. The bold lines in Fig. 1 indicate the main route of the regulation loop. The thin lines indicate the route of the disturbance: the transfer of the drug through the gastric tract into the bloodstream and to the receptor site and the transfer of information about the presence of the drug by the central nervous system to the adaptive regulator. The latter information allows the adaptive regulator to anticipate the change in the information transfer the drug will cause at the moment the drug enters the body, before it actually exerts its action on the receptor site (Grill *et. al*. 1984). The adaptive regulator will also use other information about the administration of the drug, like the time of day or the drug scene.

Fig. 2 shows a simulation with the model. A hypothetical drug is administered in equal doses over 14 days, one time a day. The parameters of the model are chosen to obtain a clear picture of

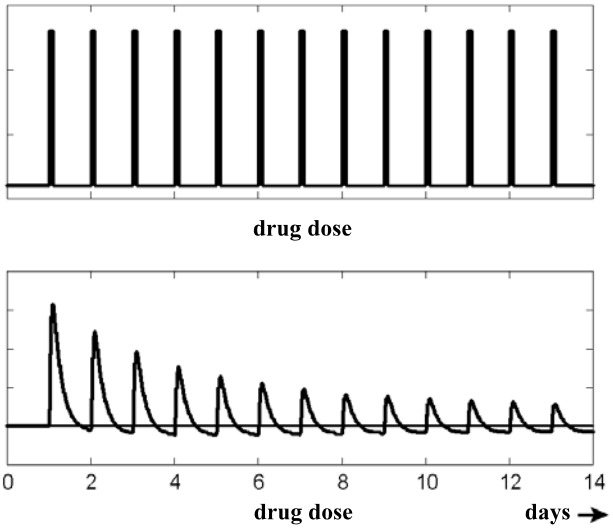

FIG. 2. Drug effect on constant drug dose. The vertical axes are in arbitrary units.

the effect. As the model does not describe a specific process, the vertical axes in all figures are in arbitrary units. The change of the sensor output caused by the presence of the drug is in the simulation assumed to be the drug effect. The simulation shows an initial large rise of the signal with respect to the base line after each administration of the drug. The level decreases when tolerance develops and settles at a magnitude determined by the parameters of the regulation loop. To compensate for the diminishing effect of a drug during tolerance development, the drug dose usually is gradually increased. This is simulated in Fig. 3: the drug dose is increased during successive administrations in such a way that the drug effect remains nearly constant. The figure shows that after tolerance has developed, a rise of the signal is followed by a drop to below the base line, representing the rebound mechanism. The magnitude of these reactions increases when tolerance to the drug increases.

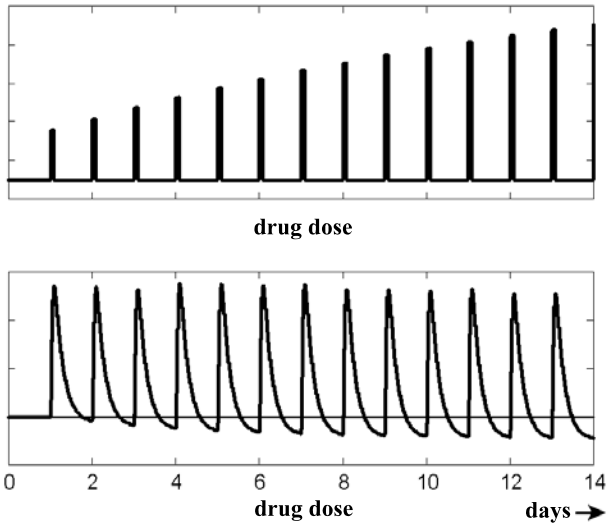

FIG. 3. Gradually increasing drug dose to obtain a nearly constant drug effect.

Optimal Protocols for Drug Withdrawal

Fig. 4 shows the difference in the effect of drug withdrawal in tolerant and addicted subjects. When only tolerance is present, the adaptive regulator, normally responsible for the partial suppression of the drug effect, will not react when no drug is present. The magnitude of the reaction following withdrawal is in this case

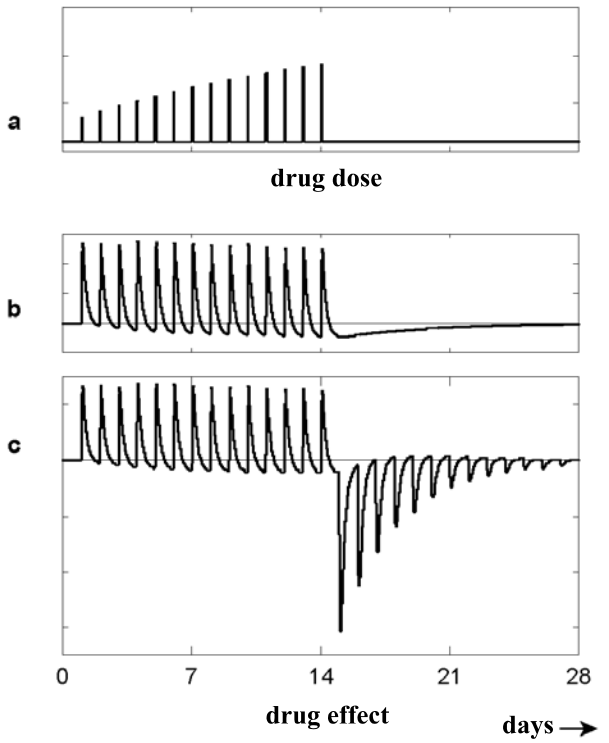

FIG. 4. Effect of drug withdrawal in tolerant (b) and addicted (c) subjects.

comparable to the regu1ar rebound during intake. When addiction has developed, the adaptive regulator, anticipating the drug intake, will respond when it "expects" the drug, causing large reactions. To obtain a clear picture of this effect, the adaptive regulator is assumed to keep responding indefinitely. In reality, only a limited number of reactions will occur. The anticipative behaviour of the organism to a drug in addiction is in the model assumed to be one of the major differences between addiction and simple tolerance. The magnitude of the reactions in addiction depends on several parameters. The most important parameter in this effect is the ability of the organism to suppress disturbances, which depends among other factors on health and age (Peper et al, 1987, 1988). The rate of suppression is reflected in the simulation in the degree of increase of the drug dose necessary to maintain a constant drug effect.

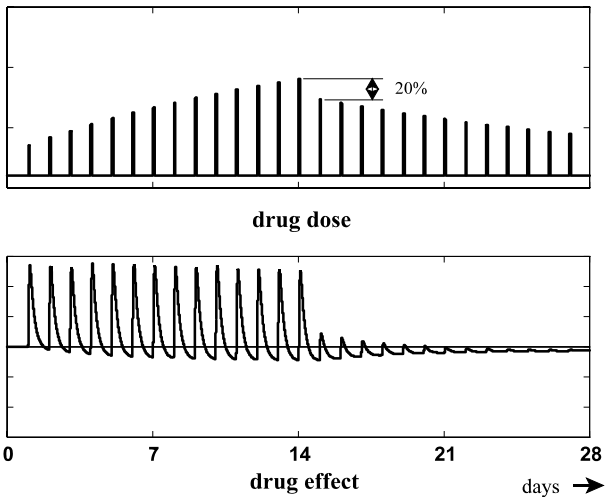

FIG. 5. Gradual drug withdrawal. A decrease of drug dose of 20% causes the drug effect in the simulation to go to about zero.

Fig. 5 shows a simulation of the way withdrawal can be achieved in addicted subjects without negative reactions. Again, as in the simulations of Fig. 2, the parameters of the model are arbitrary and chosen to obtain a clear picture of the effect. Fig. 5 demonstrates how large the effect is of small changes of drug dose: the decrease of 20% at the start of the withdrawal causes the drug effect in the simulation to go to about zero. To keep the reactions small, the decrease of the drug dose following the initial step has to equal the decrease of tolerance during the absence of the large stimuli. This is a very slow process as the simulation shows; much slower than is the case when negative reactions are allowed to occur as in Fig. 4(c). The fast decline in magnitude of the large reactions in the latter figure is due to the regulation "forcing" the reactions to zero. The slow withdrawal shown in Fig. 5 can be accelerated considerably when moderated

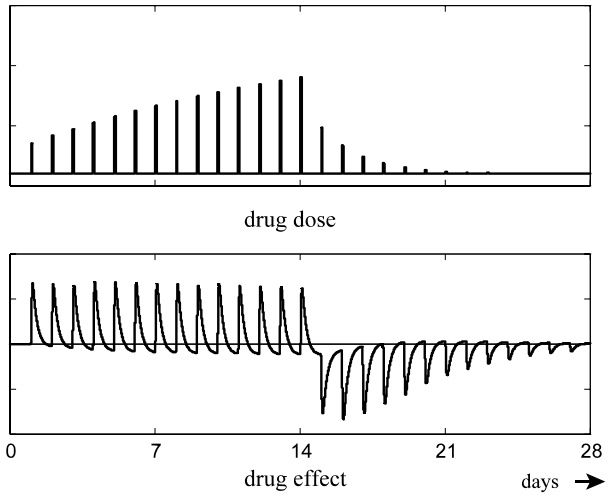

FIG. 6. Gradual drug withdrawal allowing moderate reactions.

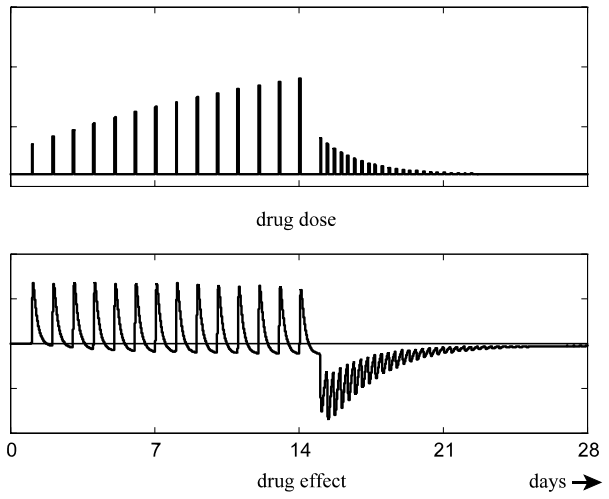

FIG. 7. Withdrawal with an increased frequency of drug application.

negative reactions are allowed. This is shown in Fig. 6, where in the simulation an initial decrease of the drug dose of about 50% is followed by a fast decrease of the drug dose to zero. The reactions in this method are considerably smaller than with abrupt withdrawal, while their decline is much faster than is the case in Fig. 5. This decline can even be accelerated when the frequency of drug administration is increased. This is demonstrated in Fig. 7 where the drug is administered three times a day: the reactions now decline considerably faster than in Fig. 6. This accelerating effect can also be made use of when

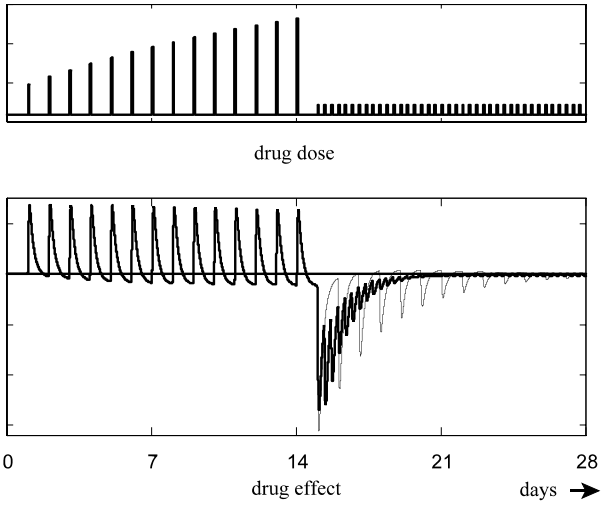

FIG. 8. Drug withdrawal with a 10% drug dose and an increased frequency of administration. Abrupt drug withdrawal is shown with a thin line.

maximal reactions are allowed in withdrawal. If the drug dose is reduced to a constant low value and the frequency of administration of the small dose is made higher than the subject is accustomed to, the reactions are about as large as in abrupt interruption of drug administration as shown in Fig. 4(c), but the speed of decline of the negative effect is considerably increased. This is demonstrated in Fig. 8, where the drug dose is lowered to 10% of the usual dose and the frequency of administration is increased from one time a day to three times a day. For comparison, abrupt drug withdrawal - as shown in Fig. 4(c) - is inserted in the figure with a thin line.

The simulations with the model suggest that there are ways in which drug withdrawal can be optimized. Clinical testing must verify the model predictions.

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