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Computer-controlled Drug Doses for IV Drug Self-administration

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Abstract

This report describes a novel procedure for computer-controlled drug-dose determination for IV drug self-administration studies. By modifying the duration of each infusion of a single concentration of a drug solution, five or more unit doses (mg/kg/inj) can be dispensed from the same syringe. The advantages of this procedure include the following: (1) it is not necessary to prepare a new syringe for each dose change; (2) the sterility of the IV catheter line is broken less often and; (3) the confounding effect of flushing through the catheter line with the previous drug dose is avoided. This procedure is accurate and reliable and can be applied to multiple sessions of any duration across days or weeks.

Keywords

Drug self-administration; Computer-controlled drug doses; Drug dose-effect curves

Introduction

One of the most effective animal models of human drug abuse is intravenous (IV) drug self-administration. It is well established that animals will self-administer most drugs abused by humans. Consequently, this model is especially useful for evaluation of drug abuse liability and for testing the effectiveness of candidate treatment medications (DEA, 2010; Fischman & Mello, 1989; Haney & Spealman, 2008; Mello & Negus, 1996).

However, IV drug self-administration is also one of the most technically challenging models to implement and maintain. Scrupulous attention to aseptic precautions in the surgical implantation of an IV catheter is required. Maintenance of catheter patency and prevention of catheter tract infection requires continuous use of aseptic procedures for replacement of drug syringes and minimal disruption of the catheter-syringe interface. In addition, IV drug self-administration procedures are very labor-intensive and require preparation of multiple syringes with several drug doses to evaluate complete drug dose- effect curves. It is well established that studies of a single drug dose can be misleading because the reinforcing efficacy of the abused drug usually follows an inverted U-shaped curve (Mello & Negus, 1996).

This report describes a technical advance that reduces risk for catheter tract infections by decreasing the number of syringe changes necessary for a drug dose-effect determination, and also significantly reduces the effort required. If the drug dose per injection is determined by computer-control of the drug volume, it is no longer necessary to prepare a different syringe for each drug dose, or to break the sterility of the catheter line to change syringes. In addition, the confounding effect of flushing the catheter line with the previous drug dose can

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be avoided. This procedure was developed for studies of IV cocaine and IV nicotine self-administration by nonhuman primates.

Methods

The usual approach to determining unit doses for I.V. drug self-administration uses a simple ratio where both drug dose and the volume delivered are fixed. The activation of the pump to pulse for one second delivers a specific volume of a drug solution. For example a 1 second pulse delivers a volume of 0.1 ml from a 60 ml syringe, and a drug concentration of 0.032 mg/kg/ml in a 60 ml syringe will deliver a dose of 0.032 mg/kg/inj. Therefore, each change in drug dose would require a new dose calculation, a change in the drug concentration, a new syringe, a break in a closed sterile IV catheter line to replace the syringe, and an IV flush to clear the catheter of the existing drug solution.

When the ratio between the drug dose and injection volume is changed, it is possible to deliver multiple doses from a single syringe. By modifying the infusion duration of a single concentration of the drug, five separate doses can be obtained. The initial relationship still exists; a syringe containing a concentration of 0.01 mg/kg/ml and a 1sec. pulse to the pump will deliver 0.1 ml or 0.01 mg/kg/inj. However, increasing or decreasing the pump duration in one-half log second increments will increase or decrease the drug dose accordingly. An infusion time of 0 sec or 0 mg/kg/inj can be used for a saline injection. Table 1 shows an example of the usual dose range used to determine a cocaine dose-effect curve.

Pump duration and dose are now virtually synonymous. The five doses listed above were carefully chosen, taking syringe pump sensitivity and time necessary to achieve the desired dose into account. A calibrated Braintree Scientific model BSP-IE pump modified with a 5 RPM motor can accurately achieve a pulse width of 0.1 seconds which is the smallest unit in the spectrum. This was measured by multiple pulse trials repeated 3,000 times. The total volume dispensed was collected in a 30 ml graduated cylinder with 0.1 ml subdivisions and a 0.1 ml tolerance. This procedure has been used successfully in this laboratory for over 6 months.

Results

Figure 1 shows data from 4 monkeys acquired with the traditional method (i.e., manually replacing syringes for each unit dose) and the computer-controlled method in which the unit dose was varied by changing the duration of the pulse that activated the drug pump. It is apparent that the U-shaped cocaine dose-effect curve was similar for both procedures. The peak of the cocaine dose-effect curve was at a unit dose of 0.01 mg/kg/inj, and higher doses fell on the descending limb of the curve. Two of the 4 monkeys took more injections of 0.0032 mg/kg/inj cocaine during the traditional than during the computer controlled dose selection method.

Discussion and Conclusions

This computer-controlled drug dosing procedure is an extension of the rapid dose effect procedure developed by Caine and coworkers in this laboratory (Caine, Negus, & Mello, 2000). In that study, computer controlled drug volume was used to administer multiple drug doses to establish a rapid dose-effect curve within a single two-hour session. Control studies showed that the volume of the injection, across a range of 0.032 ml/inj. to 1.0 ml/inj was not discriminated by the monkey.

Infusion duration across a range of 1, 3.2 and 10 sec. also did not influence the cocaine dose-effect curve. Only the unit dose of cocaine determined the shape and position of the

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dose-effect curve in three control studies that varied infusion volume/ duration (Caine et al., 2000). In the present procedure, an expanded 5 point volume range of 0.01 to 1.0 ml and a duration range of 0.1 to 10 sec was sufficient to yield unit-doses ranging from 0.001 to 0.1 mg/kg/inj of cocaine.

Caine and coworkers (Caine et al., 2000) were primarily interested in developing a procedure that could yield a complete cocaine dose-effect curve within a single 2 hour session. This approach has been successfully adapted for rats (Hiranita, Soto, Newman, & Katz, 2009) and rhesus monkeys (Bowen et al., 2003). A number of other investigators have developed methods for studying drug dose-effect curves within a single session in rhesus monkeys (Winger, Palmer, & Woods, 1989) and in rats (Emmett-Oglesby et al., 1993; Gerber & Wise, 1989; Schenk, 2002). Methods varied from using several syringes, each containing a different dose of cocaine, that could be activated by the programming circuitry (Emmett-Oglesby et al., 1993) to controlling dose by manipulating infusion durations (Gerber & Wise, 1989) to changing infusion duration and cocaine concentrations in the syringe every 30 min (Schenk, 2002).

Winger and coworkers (Winger et al., 1989) pioneered the method later modified by Caine and coworkers (Caine et al., 2000). The duration of the infusion pump pulse determined the unit-doses of the self-administered drug from a syringe containing a constant drug concentration. Infusion durations of 1, 1.7, 5.0 and 16.7 sec. resulted in one-half log unit doses of cocaine over a range of 0, 0.001, 0.003 and 0.01 mg/kg/inj. It was concluded that dose-effect curves obtained in a single session were comparable to dose-effect curves obtained when one dose of drug was examined in a single session (Winger et al., 1989).

The approach described in this report extends the application of computer-controlled drug dose selection to multiple sessions of any duration across days or weeks. Several days of exposure to a drug dose are often necessary for self-administration to stabilize (Mello & Negus, 1996). This approach can also be used to control doses of a treatment drug during evaluations lasting for several days or weeks. Because only one syringe is necessary for several unit doses per injection, the risk of catheter tract infection is reduced in comparison to changing syringes for each dose. This technology is accurate and reliable, and can be easily adapted to a number of experimental procedures.

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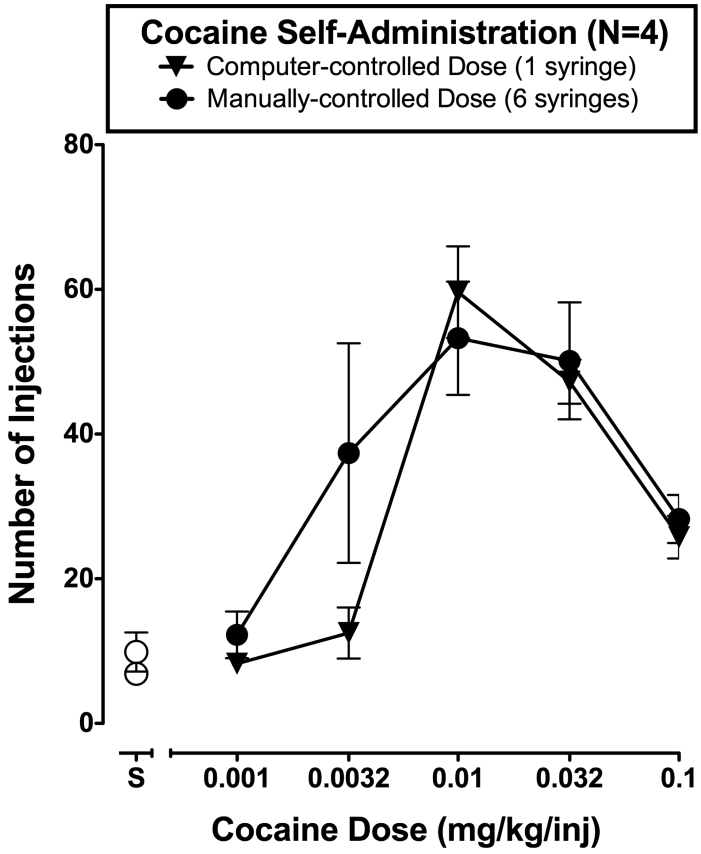

Figure 1.

Self-administration of saline or cocaine in a traditional (○,●) and a computercontrolled dosing procedure (▽,▼) in a group of four monkeys. Abscissa: Saline or cocaine unit dose (mg/kg/injection). Ordinate: Mean (±SEM) injections obtained on the last two or three days of each dose condition. The point above 'S' represents the number of injections when saline was available for self-administration.

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Table1

Concentration of Drug (mg/kg/ml)	0.1s/0.01ml (mg/kg/inj)	0.32s/0.032ml (mg/kg/inj)	1.0s/0.1ml (mg/kg/inj)	3.2s/0.32 ml (mg/kg/inj)	10s/1.0ml (mg/kg/inj)
0.01	0.001	0.0032	0.01	0.032	0.1