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Case Report Open Access

Induced Convulsion in Cynomolgus Monkeys- Combining Machine Learning and Heart Rate Variability Data to Predict GABA Receptor Antagonist

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Abstract

Drug-induced convulsion may be a severe adverse event; but, no helpful biomarkers for it are discovered. We tend to propose a replacement methodology for predicting drug-induced convulsions in monkeys supported pulse variability (HRV) and a machine learning technique. As a result of involuntary nervous activities area unit altered round the time of a convulsion and such alterations have an effect on HRV, they'll be expected by watching HRV. Within the planned methodology, abnormal changes in multiple HRV parameters area unit monitored by means that of a convulsion prediction model and convulsion alarms are issued once abnormal changes in HRV area detected. The convulsion prediction model is constructed based on multivariate statistical process control (MSPC), a well-known anomaly detection algorithm in machine learning.

Keywords: Drug; Convulsion; Monkeys; Pharmacology; Toxicology

Introduction

Drug-induced convulsion may be a severe adverse event; but, no helpful biomarkers for it are discovered. We tend to propose a replacement methodology for predicting drug-induced convulsions in monkeys supported pulse variability (HRV) and a machine learning technique. As a result of involuntary nervous activities area unit altered round the time of a convulsion and such alterations have an effect on HRV, they'll be expected by watching HRV. Within the planned methodology, abnormal changes in multiple HRV parameters area unit monitored by means that of a convulsion prediction model and convulsion alarms are issued once abnormal changes in HRV area detected. The convulsion prediction model is constructed based on multivariate statistical process control (MSPC), a well-known anomaly detection algorithm in machine learning [1].

Case report

In this study, HRV information were collected from four cynomolgus monkeys administered with multiple doses of pentylenetetrazol (PTZ) and picrotoxin (PTX), which are GABA receptor antagonists, as convulsant agents. Additionally, low doses of pilocarpine (PILO) were administered as a negative control. 12 HRV parameters in 3 hours when drug administration were monitored by mean that of the prediction model. The number and duration of convulsion alarms from HRV magnified at medium and high doses of PTZ and PTX (1/3 or 1/4 of convulsion dose). On the opposite hand, the frequency of convulsion alarms failed to increase with PILO. Although vomiting was observed in all drugs, convulsion alarms weren't related to the vomiting. Thus, convulsion alarms may be used as a biomarker for convulsions induced by GABA receptor antagonists [2-5].

We aimed to develop a new method based on HRV for predicting drug-induced convulsions. During this study, we attempted to predict convulsions in monkeys as a primary step, because electrocardiograms for HRV analysis may be recorded in animals without restriction, and HRV has been adopted for animals still as humans to monitor autonomic functions. The impact of alcohol was evaluated by means that of HRV through experiments using cynomolgus monkeys. Kerem tried to predict generalized epileptic seizures of rats based on HRV. An HRV-based ischaemic stroke detection methodology was developed utilizing a rat middle cerebral artery occlusion model. The cardiorespiratory parameters, including HRV, may be used as biomarkers for sudden unexpected death in epilepsy (SUDEP) through experiments with Kv1 [6-7].

We collected HRV data of cynomolgus monkeys treated with picrotoxin (PTX) and pentylenetetrazol (PTZ), that which are GABA receptor antagonists and area unit well-known convulsant. Additionally, pilocarpine (PILO) was administered to animals at low doses as a negative management. We applied the planned biomarker to the collected HRV information for predicting drug-induced convulsions to evaluate its validity. This study was conducted under the approval of the Institutional Animal Care and Use Committee (IACUC), printed by the National Institutes of Health. Four male cynomolgus monkeys were used because monkeys are one of the most frequently-used animals for ECG measurements in a safety pharmacology study, which is essential for drug development, and the number of animals used was determined based on the standard test protocol for safety pharmacology studies on the evaluation of the cardiovascular system in non-rodents [8].

The convulsion occurred in barely two monkeys in PTX; but, it's necessary for a biomarker to be able to find convulsion risk below the convulsion-inducing dose. Thus, this experiment and information analysis meets the aim of the study, even if not all animals had convulsions. We tend to accurately issued convulsion alarms at the medium and high doses of PTZ and PTX. The medium doses were 1/3 and 1/4 of the convulsion doses suggesting that we may predict convulsion liability while not inducement a convulsion mistreatment our prediction model. Additionally, the planned methodology expected

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a convulsion before its onset when 0.5 mg/kg of PTX was administrated. This result shows that the convulsion alarm by means that of the planned method may be used as a biomarker for drug-induced convulsions as a result the number and the total duration of convulsion alarms might indicate the potential prevalence of a convulsion within the close to future. A convulsion alarm is also issued because of ECG arti facts caused by measurement failure or cardiac arrhythmia. though we tend to visually checked the collected ECG signals around the time of convulsion alarms, no arti facts or cardiac arrhythmia had occurred, that indicates that the convulsion alarms won't are tormented by arti facts or cardiac arrhythmia during this study [9].

Many convulsion alarms occurred at 0 mg/kg-PILO administration in M2, that weren't related to the drug administration. ECG artifacts or cardiac arrhythmia weren't discovered round the time of convulsion alarm occurrences. That is, these alarms were false positives. Since changes in sleep condition considerably have an effect on HRV and should result in false positives, there is the possibility that M2 was sleeping during this measurement. Although we could not determine if the animal slept, video observation and activity count demonstrated that the animal did not move during these alarms [10].

We trained the convulsion prediction models using the three-hour data with administration between the beginnings of administration, as a result of such information won't contain sleep information during this study. On the opposite hand, we tend to collect the measurement information over 24-h during this experiment, and that we tried to coach the convulsion prediction models using the 24-h HRV information. M summarizes the number of convulsion alarms issued by the models of M1-M4 once PTX was dosed. This result shows that the number of convulsion alarms considerably magnified, significantly with 0mg/kg of PTX, whose numbers of alarms is zero. Thus, the models trained with the 24-h HRV data did not function appropriately. The 24-h data contained important changes within the activities of ANS because of feeding and sleeping; HRV data containing such changes weren't applicable for model training. Thus, the convulsion prediction model has got to be trained from HRV data throughout resting conditions, during which ANS activities don't considerably fluctuate. This indicates that the modelling data have to be selected carefully, which is a common problem in machine learning.

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