Evaluation of potassium clavulanate on ethanol consumption and decision making in the model of ethanol dependence in mice

Sir,

Glutamate increases dopamine levels in the nucleus accumbens leading to ethanol dependence. Since glutamate transporter 1 (GLT1) is responsible for the removal of synaptic glutamate, up-regulation of GLT1 attenuates ethanol consumption.[1] Rothstein *et al*. showed that beta-lactam antibiotics are potent stimulators of GLT1 expression, which is attributed to beta-lactam ring.[2] However, use of any antibiotic for a prolonged period of time for decreasing ethanol consumption may lead to the development of antibiotic resistance. Hence, an ideal agent would be one which has both, the beta-lactam ring and no antibiotic effect.It has been previously shown that impaired decision-making may be relevant to alcoholics as it may prolong their drinking habit despite the negative consequences. It is possible that serotonergic hypofunction is associated with impaired decision-making and serotonergic compounds might improve it.[3]

Potassium clavulanate has been hypothesized to decrease glutamate levels and increases serotonin levels in the central

nervous system (CNS).[4,5] Hence, the objective of this study was to evaluate effects of potassium clavulanate on ethanol consumption and decision making in the model of alcohol dependence, alone and in combination with naltrexone.

The experiment was started after approval of the institutional ethics committee. The 3-week intermittent access model of ethanol was utilized for inducing ethanol dependence.[6] Then, the mice were randomized into four groups consisting of six animals each. Group 1: Vehicle control, Group 2: 1 mg/kg/day naltrexone, Group 3: 0.1 mg/kg/day potassium clavulanate and Group 4: Naltrexone + potassium clavulanate. All the drugs were administered orally. The variables measured were ethanol and water intake/kg/day and percentage ethanol preference for 15 days after inducing ethanol dependence.

The next part was to study the effect of potassium clavulanate, alone and in combination, on the decision-making ability of ethanol dependent mice using the Iowa gambling task (IGT) [Figure 1]. The rodent version of IGT has been previously standardized in our laboratory was used for this part. In this task, animal has to choose between the advantageous and disadvantageous arms containing palatable and nonpalatable food pellets respectively. The variable is the number of choices for the disadvantageous arm.[7]

The mice in the control group exhibited intake of absolute ethanol of 20.09 ± 1.25 g/kg/day [Figure 2]. Mice in the naltrexone, potassium clavulanate, and combination group showed a significantly lesser intake of absolute ethanol as compared to control with the combination group showing the least intake of 3.27 ± 1.28 g/kg/day. The combination group showed a statistically significant lower intake of absolute ethanol when compared to the naltrexone group (7.46 ± 3.34 g/kg/day) and the potassium clavulanate group (9.81 ± 2.71 g/kg/day). Thus the combination of naltrexone + potassium clavulanate showed lower ethanol intake when compared to the individual drugs. The intake of absolute ethanol in the potassium clavulanate group was statistically comparable to the naltrexone group. Water intake in all the groups was comparable to each other which show that potassium clavulanate selectively decreased the intake of ethanol without affecting water.

Figure 1 shows that the mice in the control group exhibited 77.57 ± 5.48% of ethanol preference. The mice in the naltrexone, potassium clavulanate and combination group showed a significantly lesser percentage of ethanol preference when compared to control with the combination group showing the least preference of 26.59 ± 11.76%. The combination group showed a statistically significant lower percentage of ethanol preference when compared to the naltrexone group (51.65 ± 11.77%) and the potassium clavulanate (58.05 ± 12.24%) which showed intake of absolute ethanol. Thus, the combination of naltrexone + potassium clavulanate showed lower percentage of ethanol preference when compared to the individual drugs.

Rawls *et al*. has shown the mechanism of action of potassium clavulanate against glutamate- and cocaine-induced seizure might be mediated via decreased synaptic glutamatergic transmission.[4] This evidence generated in the earlier studies supports our proposed hypothesis about the effectiveness of potassium clavulanate in decreasing ethanol dependence.

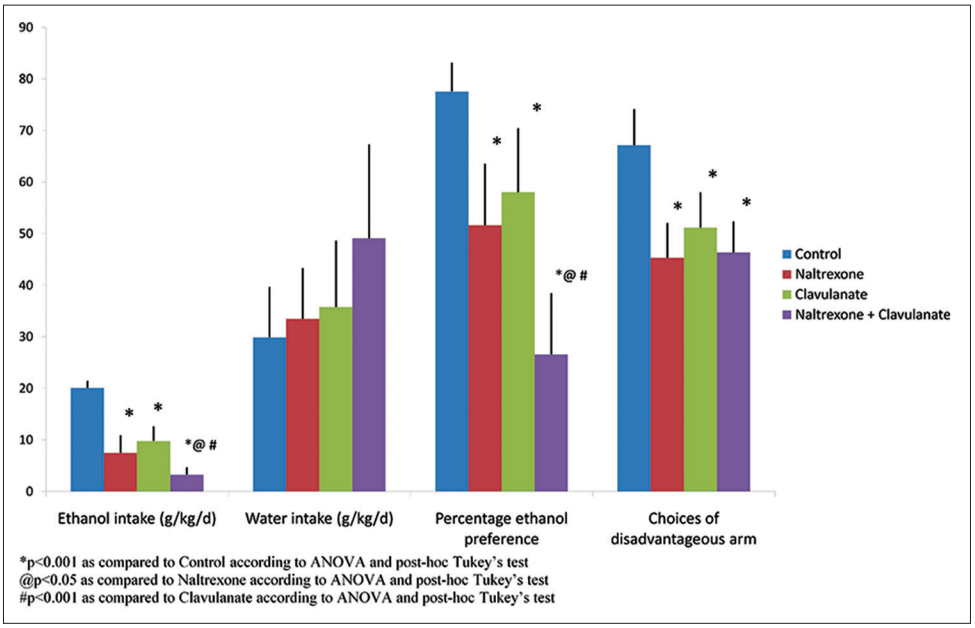

Figure 1: Effect of potassium clavulanate and its combination with naltrexone on ethanol intake, water intake, percentage ethanol preference, and number of choices on disadvantageous arm on Iowa gambling task

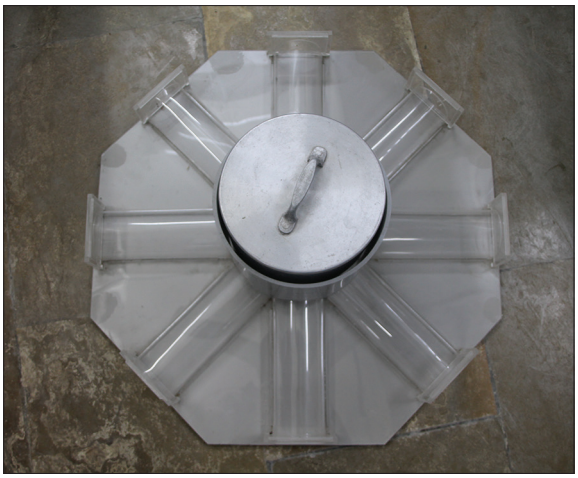

Figure 2: Rodent model of Iowa gambling task

As shown in Figure 2, the mice in the control group chose the disadvantageous arms of the IGT at a frequency of 67.16 ± 6.85 over a period of 9 days and 135 trials to each mouse. The mice in the naltrexone (45.33 ± 6.62), potassium clavulanate (51.16 ± 6.73) and combination group (46.33 ± 5.92) were observed to choose the disadvantageous arm at much lower frequency. The observations of the mice in the naltrexone group were comparable statistically to those mice in potassium clavulanate group. Furthermore, the combination group showed statistically comparable results to the naltrexone and the clavulanate groups. One can hypothesize that potassium clavulanate increases serotonin levels in the CNS, which improves decision taking abilities of alcohol dependent mice. Zeeb *et al*. have shown that 5-hydroxytryptamine 1A receptor agonist, 8-hydroxy-N, N-dipropyl-2-aminotetralin, which decreases presynaptic serotonin release impaired decision taking on IGT.[8] Increased serotonergic transmission by potassium clavulanate in the CNS might be responsible for improvement in decision-making in our experiment.

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