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Variable Dose Naltrexone-Induced Hypothalamic-Pituitary-Adrenal Stimulation in Abstinent Alcoholics: A Preliminary Study

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Abstract:

Opiate antagonists have been found to stimulate the hypothalamic-pituitary-adrenal axis. However, despite established usefulness in the management of alcoholism, systematic, oral dose-titrated naltrexone-induced hypothalamic-pituitary-adrenal stimulation has never been studied in alcoholics. Six patients (5 males, 1 female) with DSM-IV alcohol dependence, who were at least 4 weeks abstinent from any alcohol [mean 55 days (±SE 7.5)], were given four challenges of oral naltrexone (0, 25, 50, and 100 mg) in a randomized order at least 3 days apart, after an overnight fast. Naltrexone was administered at 9 AM; serum ACTH, cortisol, and prolactin were measured at time 0 and at 9 time points over the next 4 hr. Subjects also filled out a side effect questionnaire and an alcohol urge questionnaire. Physiological measurements of blood pressure and pulse rate were taken at the same time points. Repeated-measures ANOVA of the changes in serum ACTHs over time revealed a significant effect of drug (placebo vs. any dose of naltrexone) ($p < 0.05$). Post-hoc analysis revealed a significant difference between placebo and the 25 mg dose ($p < 0.01$), the 50 mg dose ($p < 0.01$), but no significance between the placebo and the 100 mg dose ($p = 0.1$). A repeated-measures ANOVA of the changes in serum cortisols over time revealed a significant effect of drug ($p < 0.01$). Post-hoc analysis revealed a significant difference between placebo and the 25 mg dose ($p < 0.01$), between placebo and the 50 mg dose ($p < 0.05$), and placebo and the 100 mg dose ($p < 0.01$). There was a significant between dose difference in pulse rate changes over baseline ($p < 0.01$), and post-hoc analysis revealed a significant diminution in pulse rate at the 100 mg dose relative to placebo ($p < 0.001$), and to the other doses. There were no significant differences in reported side effects, alcohol urge questionnaire scores, or in other physiological measurements between doses. These data suggest a significant rise in ACTH and cortisol in response to naltrexone in alcoholics compared with placebo, with no differences between 25 mg, 50 mg, and 100 mg doses, and a significant diminution in pulse rate responses at the 100 mg dose.