SUMMARY

The incidence of drug abuses in Indonesia has been increased significantly in the last few years and now bring many crucial consequences in drug induced societal and economical problems such as: tremendous high expenditures or expenses consumed for addicts rehabilitation, transmitted HIV-AIDS spreading trough opioids intravenous abusers, increasing intensity and types of criminalities. In the long run all of those serious nations problems will bring about tragical disaster of the future generation if the eradication of drug abuses would be unsuccesfull.

Morphine and other opioids derivatives are now still considered as potent drugs of abuse although the users realize that that the drugs exert potentially hazardous physical and psychological dependency effects. In the treatment of opioids dependence, several drugs are now available to the market, namely morphine antagonist (naloxone and naltrexone), and morphine substitue/surrogate" (methadone, buprenorphine). However those types of drugs seem to be innefective to stop the users from craving for opioids abuse. Using other drugs is now being considered in the purpose of reducing the unpleasant withdrawal syndromes arise from opioids abuses. The concept of the treatment is that dopamine (DA), serotonine (5HT) and norepinephrine (NE) release in the brain area (mesocorticolimbic dopamine system) are the neurotransmitter responsible for opioids addiction and withdrawal syndromes. The available drugs having activities on those neurotransmitters are antipsychotics drugs of typical class (blocking action on D_2 receptor) namely haloperidol, sulpiride, chlopromazine; and also the atypical class (act on D_2 receptor as well as $5HT_{2A}$ receptor) namely clozapine and risperidone. The superiority of the atypical class to that the typical one was the atypical antipsychotics exert lower/no risk of extrapyramidal side effects like ataxia, dyskinesia etc.

Based on the above concept, this study was aimed to elaborate the effect of atypical and typical antipsychotics in reducing morphine withdrawal syndromes. Study was conducted on 84 male mice aged 4 months, weighed 26-31 grams. The mice were divided into 14 groups of 6 mice each. Group I (MOR) as control

(treated with morphine injection s.c and water orally), and group 2 (PLA) as placebo (treated with normal saline injection and water orally). The other 12 groups were treated by morphine injection s.c and antipsychotics orally).

The first step was all group except PLA receive morphine HCl s.c with cronic escalating dose twicw a day of 10,20,40,80,100,120, 140 mg/kg for 8 consecutive days to induce morphine dependence. The second step was each group receive the following dose of antipsychotics orally: for the groups of chlorpromazine (CPZ) dose of CPZ(i) 5 mg/kg bw; CPZ (ii) 10 mg/kg bw; CPZ (iii) 30 mg/kg bw; for the groups of clozapine (CLO) dose of CLO(i) 10 mg/kg bw, CLO(ii) 15 mg/kg bw, CLO(iii) 20 mg/kg; for the groups of risperidone (RIS) the dose of: RIS(i) 1 mg/kg bw, RIS(ii) 4 mg/kg, RIS(iii) 8 mg/kg bw; for the groups of haloperidol (HAL) dose of HAL(i) 1 mg/kg bw, HAL(ii) 4 mg/kg bw and HAL (iii) 10 mg/kg bw. During the experimental studies the animal were located in then ormal room temperature, feeding and watering were readily available in the cages. The third step was naloxone injection 12 mg/kg bw i.p were given to all groups 2 hours after the last morphine injection on the day 8^{th} to praecipitate withdrawal syndromes.

The withdrawal syndromes in mice were observed for readily after naloxone injection for 15 minutes accoin 20 x 20 cm transparent cage according to Gellertz Holtzman withdrawal rating score. Data obtained were analyzed for normal distibutions of the populations, the parameter of effects using Fischer exact test, U Mann Whitney test, One way ANOVA and linear regression corelation.

The result of study revealed that both class of the antipsychotics reduced some of morphine withdrawal signs such as; erection, swallowing movement, and weight loss. Total Gellertz Holtzman rating score decreased to the range of 33,3% - 61,1 %. In addition, (RIS) risperidone reduced hyperlocomotion better than other antipsychotics used in this study, where as (CLO) Clozapin and (CPZ) chlorpromazine resulted in better response in reducing wet dog shakes effect than haloperidol (HAL) and risperidone (RIS). Antipsychotics, both typical and atypical in combination with other agents like NMDA antagonist (dextrometorphan) kappa agonist agent, alpha-2 agonist (clonidine) might be

considered to attenuate withdrawal syndrome due to opioid abuse " as empirical" step but further study required for the safety and efficacy aspects of the drugs.

ABSTRACT

This study was aimed to elaborate the effect of atypical and typical antipsychotics chlorpromazin (5,10, 30 mg/kg), haloperidol (1, 4, 10 mg/kg) clozapin (10,15, 20 mg/kg) and risperidon (1,4, 8 mg/kg) in reducing morphine withdrawal syndromes. Body weight loss during morphine pre treatment, diarrhea incidence, abdominal constriction and wet dog shakes was not prevented by all antipsychotics. Clozapin (10, 20 mg/Kg), risperidon (1,4 mg/kg), chlorpromazin (10, 30 mg/kg) could decrease swallowing movement. Exept clozapin 20 mg/kg all antipsychotics attenuated erection incidence. Risperidone (1,4,8 mg/kg) and chlorpromazine 30 mg/kg significantly attenuate 'attempt to escape' behaviour. Body weight loss during morphine withdrawal that measured one hour after naloxone injection.was prevented by both typical and atypical except chlorpromazine 5 mg/kg and haloperidol (1,4 mg/kg) and they both could decrease morphine withdrawal syndrom score according Gellertz Holtzman withdrawal rating score.

In conclusion, both class of the antipsychotics reduced some of morphine withdrawal signs such as; erection, swallowing movement, and weight loss. Total Gellertz Holtzman rating score decreased to the range of 33,3% - 61,1 %. In addition, (RIS) risperidone reduced hyperlocomotion better than other antipsychotics used in this study, where as (CLO) Clozapin and (CPZ) chlorpromazine resulted in better response in reducing wet dog shakes effect than haloperidol (HAL) and risperidone (RIS).

Keywords: atypical, typical antipsychotics, morphine, withdrawal syndrome, Gellertz-Holtzman withdrawal rating score, mice