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Extrapyramidal and purgative effects of fluphenazine in turkeys

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Fluphenazine is a typical antipsychotic medicine with extrapyramidal effects. It was tested for purgative and neurological effects in turkeys. The results showed that the drug induced purgation at a dose range of 5 to 200 mg/kg body weight causing highest frequency of fecal droppings (7) at 10 mg/kg in 7 min and lowest frequency of dropping (1) at 50 mg/kg. However, the number of fecal droppings was not linearly correlated with dose progression. Fluidity of the dropping increased with dose. This effect may be due to the stimulation or sedation of gastrointestinal tract. At 5 mg/kg, the animals were calm, but at 15 mg/kg of fluphenazine, there was severe torticollis as the dose increased. In conclusion, fluphenazine has hormetic dose response of gastrointestinal stimulation and inhibition as well as central nervous system depression and stimulation, respectively.

Key words: Fluphenazine, purgation, extrapyramidal effect, acetylcholine, sedation.

INTRODUCTION

Hormesis is a phenomenon of biphasic dose response characterized by exhibiting stimulatory or beneficial effects at low doses and inhibitory or toxic effects at high doses (Bao et al., 2015). Fluphenazine, a phenothiazine, was one of the first drugs to be classified as an antipsychotic and was approved by the Food and Drug Administration in 1959. In Britain, it was first used for the relief of anxiety (Matar et al., 2013). It causes elevated liver enzymes during management of delirium in infants (Turkel et al., 2013). Fluphenazine was on the World Health Organization (WHO) list of Essential Medicines of 2009 (Cieslik-Boczula et al., 2014). It reduces proteotoxicity in *C. elegans* and mammalian models of alpha-I-antitrypsin deficiency (Li et al., 2014). Fluphenazine can also be used for the treatment of Tourette syndrome (Wijemanne et al., 2014). Effectiveness trials and cost-effective analysis have caused first-generation antipsychotics to be re-examined regarding place in therapy. Plasma level of fluphenazine could be detected 4 months after the last administration with severe extrapyramidal symptoms, which is resolved by titrating 4 mg/day of benztropine within 72 h. This suggests complex pharmacokinetic properties of long-term fluphenazine decanoate treatment and the adverse

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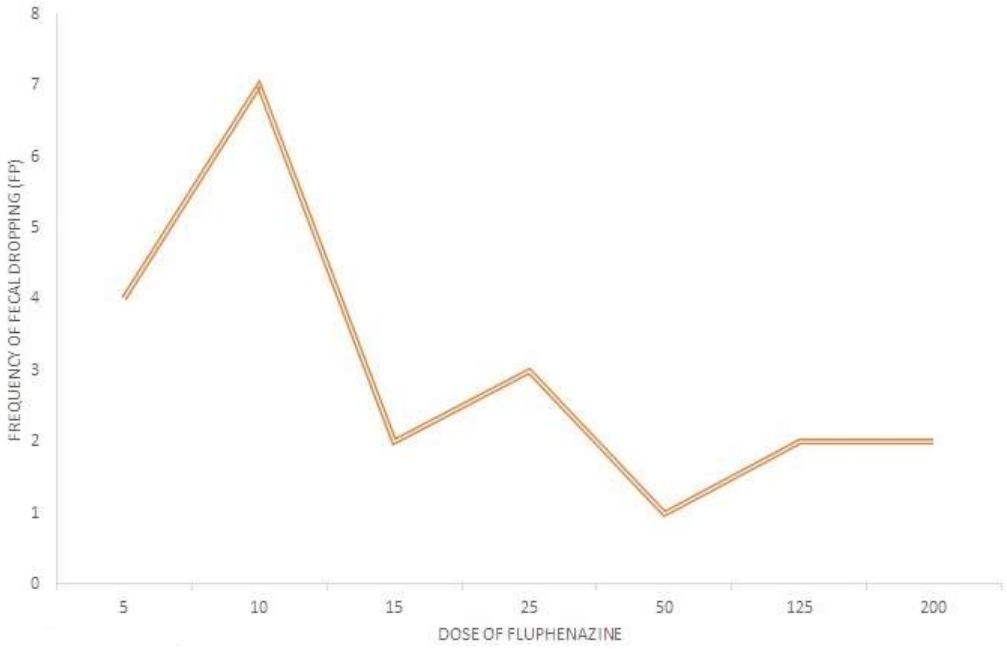

Figure 1. Frequencies of fecal dropping per milligram of fluphenazine.

effect resulting from dopamine D_2-receptor antagonism (Purvis et al., 2012).

Many of the problems that occur when patients are changed from oral depot fluphenazine are caused by high dosages; therefore low-dose treatment strategies are required in schizophrenia (Levine, 1980). Fluphenazine hydrochloride induces the formation of a small population of rod-like fibrils that differ from the characteristic ribbon-like fibrils normally observed for APOC-II (Zlatic et al., 2015). It is used in race horses as performance-enhancing drug, and for that reason, it has been banned by the Association of Racing Commissioners International (Costello et al., 2013). Hence, intramuscular fluphenazine was investigated in healthy turkeys.

MATERIALS AND METHODS

Seven female turkeys of 12 weeks old and weighing 2.1±0.5 kg were purchased from a commercial turkey raiser in Makurdi, Nigeria and kept in the laboratory of the Department of Veterinary Physiology, Pharmacology and Biochemistry, University of Agriculture, Makurdi, Nigeria. The turkeys were acclimatized for two weeks and thereafter intramuscularly administered 5, 10, 15, 25, 50, 125 and 200 mg/kg body weight of fluphenazine; it was observed for a period of 30 min and thereafter for 24 h. Neurological signs and number of fecal droppings from the turkeys were recorded. Feed and water were provided *ad libitum*. All the animals were handled according to the international guiding principles for biomedical research involving animals (CIOMS, 1985) as certified by University of Agriculture Makurdi Ethical Committee on the use of laboratory animals. All the turkeys were fed a commercial feed (Grower®) produced by Grand Cereals and Oils Limited (GCOML) Jos, Nigeria. Clean water was provided *ad libitum*.

RESULTS AND DISCUSSION

The number of fecal droppings at various doses were 4 (5 mg/kg), 7 (10 mg/kg), 2 (15 mg/kg), 3 (25 mg/kg), 1 (50 mg/kg), 2 (125 mg/kg) and 2 (200 mg/kg) body weight, respectively (Figure 1). The purgative effect stopped at the end of 10 min of observation. Pearson correlation of -0.4 showed that the number of fecal droppings was not linear with dose progression (that is the number of droppings was loosely scattered away from the line). But, there was a weak correlation of 16% (r^2 = 0.16) between dose of fluphenazine and frequency of fecal droppings, signifying that it may be used to remove ingested toxicant within a very short period of time. The purgative effect may be due to intestinal stimulation associated with fluphenazine (Peryriere et al., 2009). However, the probability of one fecal dropping from healthy turkey in 10 min was $^1/_7$. The 10 mg/kg of fluphenazine caused 7 fecal droppings in 7 min but at 15, 125 and 200 mg/kg, the frequency of fecal droppings was 2, at 50 mg/kg there was one frequency of fecal dropping in 7 min. Other signs observed were standing still, opisthotonos, calmness, torticollis and hyperventilation (Figures 2 to 8). The findings agree with the report of Calabrese (2006) indicating that anxiolytics have predominantly hormetic dose response and represent the most fundamental and common dose-response model in

Figure 2. Standing still (5mg/kg) torticollis (15 mg/kg).

Figure 4. Recumbent and torticollis (15 mg/kg).

Figure 3. Calm (10 mg/kg).

Figure 5. Torticollis (25 mg/kg).

the biomedical and toxicological sciences. They have important implications for the process of drug discovery development, clinical evaluation, and quantitative expectation of drug treatment effects (Calabrese, 2006).

A common feature of these drugs is that they act via inverted U-shaped dose response, consistent with the hormetic dose response model at described window (Calabrese, 2008). The depression at 5 mg/kg and torticollis and opisthotonos from 15 to 200 mg/kg show that as the dose is reduced, the response is increased, therefore having two distinct phases-biphasic and non-monotonic (Hayes, 2006). But, the idea that low dose effects may be different is accepted and questionable (Mattson and Cheng, 2005). Fluphenazine can increase action potential duration and induce QT prolongation in several animal models and humans, as the block of cardiac human ether-a-go-go-related gene (hERG) channels is one of the leading causes of acquired long

Figure 6. Recumbent and torticollis (125 mg/kg).

Figure 7. Hyperventilation and Opisthotonos (50 mg/kg).

Figure 8. Severe torticollis (200 mg/kg).

QT syndrome (Hong et al., 2013).

Levinson (1990) reported that antipsychotic effects of fluphenazine are in graded fashion and doses greater than 0.2 mg/kg per day were associated with greater clinical improvement, but also with a high incidence of extrapyramidal symptoms. But doses over 0.3 mg/kg per day were associated with more severe extrapyramidal symptoms, suggesting a linear relationship between fluphenazine dosage and acute outcome, and this relationship is observed in patients whose conditions improve to a criterion level (Levinson et al., 1990). CNS agents may have both excitatory and sedative effects (Saganuwan, 2017a) which may be dependent on metabolite (Saganuwan, 2017b), functional group of the compound (Saganuwan, 2017c), polymeric carriers of the CNS agents (Saganuwan,2017d) and their physicochemical and structure activity properties (Saganuwan, 2016). Fluphenazine decanoate produces fewer movement disorder effects than fluphenazine enanthate (Maaxam et al., 2015). Both are effective antipsychotics for treating schizophrenia. The benefits gained by long acting preparations may be offset by a higher incidence of adverse effects . Though the use of depot fluphenazine continues to be based on clinical judgement rather than evidence from methodical evaluation within trials (Adams et al., 2006), fluphenazine decanoate and enanthate may be associated with equal or more side effects than oral fluphenazine (Zhornitsky and Stip, 2012).

Intramuscular injections offer an advantage over oral medications for treating schizophrenia by reducing poor compliance (Maaxam et al., 2015). Fluphenazine plasma levels above 1.0 ng/ml and doses above 0.2 to 0.25 mg/kg per day showed better activity (Levinson et al., 1990).

Fluphenazine decanoate is a long-acting phenothiazine neuroleptic that attenuates the stress response and may be useful during intensive handling for reproductive procedures in non-domestic ungulates and elevate serum prolactin, which can suppress fertility in some species (Weiss et al., 2014). But, the first dropping at 125 and

200 mg/kg was soft,and the second dropping was watery. The volume of excreta increased with the dose, but the frequency of dropping decreased with the increased doses, a typical phenomenon of hormetic dose response.

In this study, the most effective purgative dose was 10 mg/kg which caused 7 fecal droppings. At 15 mg/kg, the number of fecal droppings reduced to 2. This finding agrees with the report of Maaxam et al. (2015) indicating that fluphenazine (12.5 mg/day) treatment was discontinued due to lack of efficacy and adverse effect (Conley et al., 2005).

Conclusion

Fluphenazine has extrapyramidal and purgative effects in turkeys. The purgative action may be by stimulation or sedation of gastrointestinal tract activity. Therefore, fluphenazine may be used to remove toxic ingesta from the gastrointestinal tract of turkeys in a very short possible time.

CONFLICT OF INTERESTS

The author has no conflict of interest whatsoever.

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