

*Full Length Research Paper*

# Effect of sertraline on the antidepressant-like actions of furosemide and bumetanide in the FST and TST in mice

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Accepted 06 March, 2012

The objective of the study was to determine the effect of sertraline on the antidepressant-like responses of furosemide and bumetanide in the forced swim test (FST) and tail suspension test (TST) in mice. Groups of mice were treated for 30 days with placebo, furosemide (10mg/kg) + sertraline (5mg/kg), bumetanide (2.5mg/kg) + sertraline (5mg/kg) respectively. Experiments were done on Days 1, 15 and 31 in the FST and TST to determine the effects of the agents on duration of immobility. In the FST, results showed that in the test groups, furosemide and bumetanide potentiated the prolongation of the period of onset of immobility of sertraline significantly when acute values were compared to control values ( $F(2, 15) = 6.82, P < 0.05, < 0.01$ ), when subchronic values were compared to acute values ( $F(2, 15) = 9.67, P < 0.05, < 0.01$ ) and when chronic values were compared to subchronic value ( $F(2, 15) = 13.89; P < 0.05, < 0.01$ ). These results were comparable to the experimental results obtained in the TST. In conclusion, results show that subchronic and chronic furosemide administration significantly potentiated the reduction of immobility in the FST and TST of chronically-administered sertraline more than bumetanide administration.

**Key Words:** Furosemide, Bumetanide, Sertraline, FST, TST

## INTRODUCTION

Accumulating evidence indicates that the loop diuretics, furosemide and bumetanide, possess neuroprotective effects (Malek et al., 2003; Nabekura et al., 2002) and, in particular, that furosemide may enhance long-term potentiation (Wang et al., 2006). Antidepressants enhance long-term potentiation (Zaman and Zaman, 2001; Norman et al., 2007) and both furosemide and bumetanide could affect long-term potentiation by effects on the brain renin-angiotensin system. Angiotensin II and the angiotensin peptides 4 and (1-7) may influence the polarity of long-term potentiation/long-term depression (Kramar et al., 2001; Tchekalarov and Albrecht, 2007) inverted by stress. Also the effect of furosemide and bumetanide on angiotensin could enhance CREB-BDNF signalling since angiotensin II elevates CREB levels by 100%

(Holownia and Braszko, 2007) and angiotensin peptides are intimately related to neurotransmitter release mechanisms at the nerve endings (Yamada et al., 2002).

With respect to neurotrophins, chronic furosemide-induced BDNF mRNA synthesis is increased by angiotensin (Szekeres et al., 2010) and the neuron-specific cation chloride co-transporter,  $KCC_2$ , that is upregulated in depression (Matriciano et al., 2010) is down-regulated by both furosemide and BDNF to cause inhibition of GABA (Wardle and Poo, 2003). Bumetanide has relatively no effect on  $KCC_2$  (Xie et al., 2003) and is considered specific for  $NKCC_1$ .

Also, the antioxidant (Hamelink et al., 2005), phosphodiesterase inhibiting (Marcus et al., 1978) and anti-apoptotic effects (Wang et al., 2007) of furosemide could have additive or synergistic effects with those of sertraline (Kumar and Kumar, 2009; Anacker et al., 2011; Bah et al., 2009), a selective serotonin reuptake inhibitor (SSRI), presently used as antidepressant, to enhance cAMP-CREB- BDNF-ERK 1/2-Bcl-2 signalling.

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Bumetanide may also possess antioxidant effects (Geng et al., 2009) since it down-regulates, like furosemide, the inwardly-directing sodium-potassium-chloride co-transporter (NKCC<sub>1</sub>), thereby attenuating the effects of the oxidative stress-response kinase (OSRK<sub>1</sub>) in activating NKCC<sub>1</sub>. Evidence has been shown that furosemide administration down-regulates the dopamine transporter (Lucas et al., 2003) and studies suggest a functional cooperation exists amongst serotonergic, noradrenergic and dopaminergic systems in the brain (Vizi et al., 2003).

The aim of the study was to evaluate the effects of sertraline on the antidepressant-like responses of furosemide and bumetanide in the FST and TST in mice.

## MATERIALS AND METHODS

Male albino mice (25-35g) were used. Groups of mice were housed in the University's departmental laboratory in separate plastic cages for four weeks prior to testing. Animals were housed at room temperature of 25<sup>o</sup>-27<sup>o</sup>C in a 12-hour light/dark cycle. They were given pretreatments of intraperitoneal injections, allowed food and water *ad libitum*, and on the day of the test transported to the sound-proof testing area in their own cages. All drugs were supplied by Sigma-Aldrich through Rovet Chemicals, Benin –City, Nigeria. All the drugs were dissolved in 10% Tween 80 in distilled water because of furosemide's solubility. The mice were injected intraperitoneally (i.p.). The doses of drugs were chosen from previous studies (Eraly et al., 2006; Luszczki et al., 2003; Cryan et al., 2004; Kosuda et al., 1997; Hesdorffer et al., 2001; Aburawi et al., 2007).

### Drug studies with the forced swimming test

Male albino mice (25-35g), after pre-treatments and acclimatisation in the departmental laboratory were transported to the sound-proof testing area in their own labelled cages. They were allowed to adapt for one hour before the intraperitoneal injections after which there was a wait-period of 60 minutes before the tests of immobility.

Mice were forced to swim for four minutes in a vertical glass cylinder of height 27cm, diameter 16.5cm and containing fresh tap water to a depth of 15cm at 27<sup>o</sup>C. A behavioural model of immobility first postulated by Porsolt, (1977) and named the behavioural despair model was used. In this model, mice are forced to swim in a restricted space from which escape is not possible. Following an initial period of vigorous activity, the mice become helpless and adopt a characteristic immobile posture with no further attempt to engage in escape-related behaviour; and this reflects a state of despair or lowered mood. The period of on-set of immobility is timed by an observer unaware of the drug given and

recorded.

In this experiment, the mice were pre-treated i.p. according to the following protocol:

Group 1 received 0.25 ml of placebo daily for 30 days

Group 2 received 5mg/kg of sertraline + 2.5mg/kg of bumetanide daily for 30 days

Group 3 received 5mg/kg of sertraline + 10mg/kg of furosemide daily for 30 days

Tests were done on Days 1 (acute), 15 (subchronic) and 31 (chronic) when the dose of furosemide was increased to 100mg/kg and that of bumetanide to 75mg/kg but the dose of sertraline remained unchanged.

### Drug studies with the tail suspension test

Male albino mice weighing 25-35g were used. They were housed in the departmental laboratory in labelled metal cages for 30 days prior to testing, in a 12-hour light/dark cycle with food and water freely available. The mice were transported from the housing room to the sound-proof testing area in their own cages and allowed to adapt to the new environment for one hour before testing. The groups of mice were treated with the test compounds by intraperitoneal (i.p.) injection one hour prior to the test of immobility. In the TST first formulated by Steru et al (1985), the mice are suspended on the edge of a shelf 58cm above a table-top by adhesive tape placed approximately 1cm from the tip of the tail. The duration of immobility is recorded for a period of 5 minutes by an observer unaware of the test compound

In this experiment, the mice were pre-treated i.p. according to the protocol adopted for the FST.

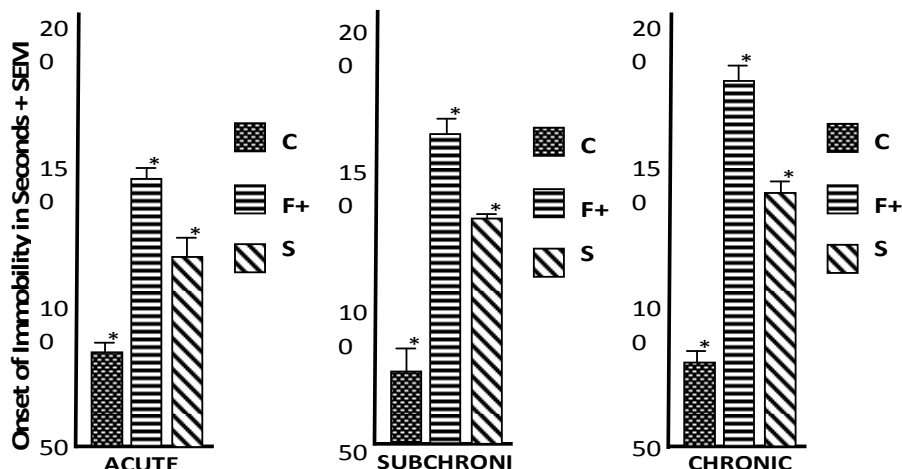
Tests were done on Days 1 (acute), 15 (subchronic) and 31 (chronic) when the dose of furosemide was increased to 100mg/kg and that of bumetanide to 75mg/kg but the dose of sertraline remained unchanged.

### Statistical analysis

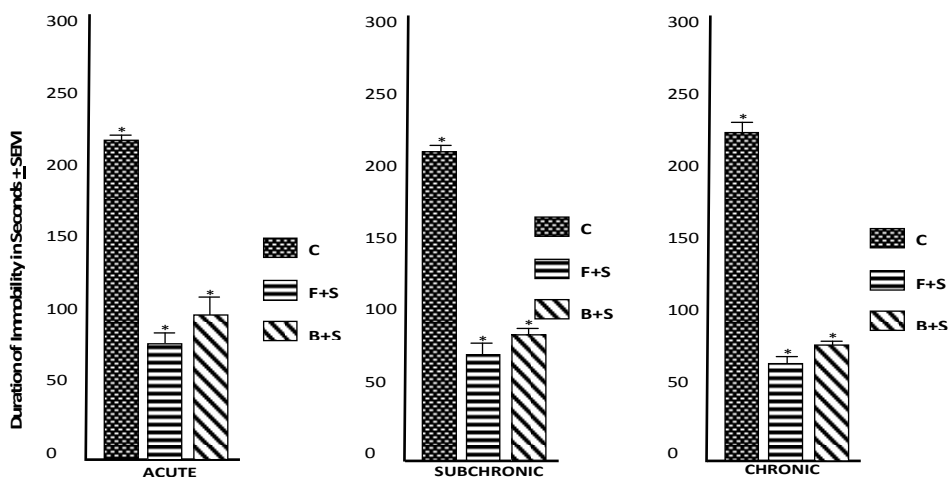
One-way ANOVA was applied followed by DMR as post-hoc test. Mann-Whiney non-parametric test was used when comparing the means of only two samples. The difference was considered to be significant at  $P < 0.05$ , ( $< 0.01$ ).

## RESULTS

In the FST (Figure 1), while the onset of immobility in the control group was  $43.75 \pm 1.04$  seconds, the combination of furosemide (100mg/kg) + sertraline (5mg/kg) prolonged the onset to  $125.90 \pm 1.33$  seconds at Day 1 (acute), to  $150.00 \pm 2.00$  seconds at Day 15 (subchronic) and to  $177.90 \pm 2.89$  seconds at Day 31 (chronic). The response at Day 31 was a synergistic



**Figure 1.** Effect of sertraline on the acute, subchronic and chronic antidepressant-like actions of furosemide and bumetanide in the fst in mice. The vertical bars represent the values in seconds  $\pm$  S.E.M. The furosemide + sertraline and bumetanide + sertraline combination at the doses shown significantly prolonged the period of onset of immobility of mice when acute values are compared to control values ( $F(2, 15) = 6.82$ ; ( $P < 0.05$ ,  $< 0.01$ ), when subchronic values are compared to acute values ( $F(2, 15) = 9.67$ ; ( $P < 0.01$ ) and when chronic values are compared to subchronic values ( $F(2, 15) = 13.89$ ; ( $P < 0.05$ ,  $< 0.01$ ). At the three instances, the post-hoc DMR test showed the furosemide + sertraline combination to be most significant.



**Figure 2.** Effect of sertraline on the acute, subchronic and chronic antidepressant-like actions of furosemide and bumetanide in the tst in mice. The vertical bars represent the values in seconds  $\pm$  S.E.M. The furosemide + sertraline and bumetanide + sertraline combinations at the doses shown significantly enhanced the reduction of immobility of mice when acute values are compared to control values ( $F(2, 15) = 7.63$ ; ( $P < 0.05$ ,  $< 0.01$ ), when subchronic values are compared to acute values ( $F(2, 15) = 12.34$ ; ( $P < 0.05 < 0.01$ ), and when chronic values are compared to subchronic values ( $F(2, 15) = 19.05$ ; ( $P < 0.05$ ,  $< 0.01$ ). At the three instances, the post-hoc DMR test showed the furosemide + sertraline combination to be more significant.

response because it was more than the sum of the individual responses. The bumetanide (75mg/kg) + sertraline (5mg/kg) combination prolonged the period of onset of immobility to  $86.65 \pm 1.19$  seconds at Day 1 (acute),  $104.80 \pm 0.80$  seconds at Day 15 (subchronic)

and to  $116.30 \pm 1.29$  seconds at Day 31 (subchronic). Statistical analysis showed the combinations prolonged the period of onset of immobility significantly when acute values were compared to control values ( $F(2, 15) = 6.82$ ;  $P < 0.05$ ,  $< 0.01$ ), when subchronic values were

compared to acute values ( $F(2, 15) = 9.67$ ;  $P < 0.05$ ,  $< 0.01$ ) and when chronic values were compared to subchronic values ( $F(2, 15) = 13.89$ ,  $P < 0.05$ ,  $< 0.01$ ). At the three instances, post-hoc DMR test showed the furosemide + sertraline combination to be more significant. In the TST (Figure 2), while the duration of immobility in the control group was  $211.72 \pm 4.39$  seconds, the combination of furosemide (100mg/kg) + sertraline (5mg/kg) reduced the duration of immobility to  $79.39 \pm 4.50$  seconds at Day 1 (acute), to  $77.80 \pm 1.31$  seconds at Day 15 (subchronic) and to  $61.01 \pm 0.88$  seconds at Day 31 (chronic). The bumetanide (75mg/kg) + sertraline (5mg/kg) combination reduced the duration of immobility to  $100.70 \pm 3.36$  seconds at Day 1 (acute),  $86.42 \pm 5.27$  seconds at Day 15 (subchronic) and to  $80.39 \pm 0.90$  seconds at Day 31 (subchronic). Statistical analysis showed the combinations prolonged the reduction of immobility significantly when acute values were compared to control values ( $F(2, 15) = 7.63$ ;  $P < 0.05$ ,  $< 0.01$ ), when subchronic values were compared to acute values ( $F(2, 15) = 12.34$ ;  $P < 0.05$ ,  $< 0.01$ ) and when chronic values were compared to subchronic values ( $F(2, 15) = 19.05$ ,  $P < 0.05$ ,  $< 0.01$ ). At the three instances, post-hoc DMR test showed the furosemide + sertraline combination to be more significant.

## DISCUSSION

Results show that subchronic and chronic furosemide + sertraline administrations significantly enhances the reduction of immobility ( $P < 0.05$ ,  $< 0.01$ ) in the FST and TST models of depression using mice over that of the acute administration, and over that of the bumetanide + sertraline combination. The furosemide + sertraline combination showed synergy after 30 days of treatment of mice. The diuretic and renin-releasing effects of furosemide seems to have no major relationship to its demonstrated anti-depressant-like activity for furosemide showed a more significant antidepressant-like efficacy compared to bumetanide even though bumetanide is a more potent diuretic (Ramsay et al., 1978) and shows a greater effect in inducing renin release (Scholz et al., 1993).

Bumetanide's effects in preventing apoptosis (Marklund et al., 2001) may enhance cell resilience and neuroplasticity but again, the Bax blocker, furosemide has more effects as it reduces the Bax/Bcl-2 ratio (Sanchez-Gomez et al., 2011). The more robust antioxidant status of furosemide and its free radical-scavenging effects (Lahet et al., 2003) means that furosemide is able to, more potently, attenuate excitotoxicity mediated by reactive oxygen species caused by sustained  $Ca^{2+}$  increases due to glutamate, AMPA and kainite receptors (Sanchez-Gomez et al., 2011) and this attribute of furosemide may partially explain its synergy with sertraline in our experiments. Additionally, furosemide's activation of the endogenous

antidepressant enkephalin/ $\mu$ -opioid receptor system (Grondin et al., 2011), an attribute bumetanide has not been reported to share, may enhance its antidepressant-like actions.

The phosphodiesterase- and adenosine-inhibiting actions of furosemide (Marcus et al., 1978; O'Connor et al., 1991) could enhance those of sertraline and increase cAMP-CREB-BDNF signaling. Furosemide inhibits adenosine with more efficacy than bumetanide (Polosa et al., 1993).

By its effect as a  $KCC_2$  downregulator (Wang et al., 2006), an attribute it shares with BDNF (Wardle and Poo, 2000), furosemide may enhance CREB-BDNF signalling and induce neurogenesis (Roitman et al., 2002), an important factor in the induction of long-term potentiation.

The synergistic effect furosemide + sertraline displayed from our experiments may find further explanation at a down-stream level involving BDNF release since furosemide upregulates BDNF production which can synergise with serotonergic agent (Deltheil et al., 2009) and secondly, the serotonergic system has been found (Kozisek et al., 2004) to mature earlier than the noradrenergic system.

We have shown in a previous report that furosemide enhances noradrenergic signalling to mediate its effects. This action of furosemide could synergise with serotonergic signalling mediated by sertraline to cause the synergistic response observed in our experiments.

In conclusion, results of the experiments provide evidence that chronic administration enhances the effect of furosemide + sertraline combination above that of bumetanide + sertraline combination in reducing immobility of mice in the FST and TST models of depression.

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