Acetaminophen Mimics the Action of Salbutamol in Relaxing Gravid Human Uterus - In - Vitro

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Summary:

Management of preterp'labour generally treated by salbutamol even with some expected disturbing maternal pulmonary oedema , respiratory distress and cardiovascular side effects and neonatal low-sized and cellularity of thymus and lymph nodes . This demands finding a substitute free of these side effects . Initially, acetaminophen was tested on rats uterine horns and on pregnant rats and reported an effective relaxation of the uterine horns and profound delay in parturition . These results jestified an in-vitro study on strips of gravid human uterus ruptured during difficult labour. Acetaminophen (50 mg) reduced tension by 50% which was comparable decrease in tension when 5 gg of salbutamol was added. Profound drop in tension when adjunct use of both drugs, while repeated three doses of 50 mg acetoaminophen were added separately resulted in corresponding drops in tesion down to below resting level . These findings encouraged future clinical trials on threatened women with abortion since the use of acetaminophen in the usual dosage is effective tocolytic agent without any maternal side effect but with mild possible neonatal lung congestion as a result of transient narrowing of ductus arteriosis especially in advanced gestation age.

Key Words: Acetaminophen, Salbutamol, Human Uterus

Introduction:

Acetaminophen which is the active ingredient of paracetamol or panadol tablets had mild central analgesic property besides being effective antipyretic similar to aspirin, (I). Aspirin and indomethacin can inhibit prostaglandins-PG (PG-E, PGI and thromboxime) biosynthesis and release, (2). Myometrial tone is controlled by continuous presence of PG-E2 (3), while the administration of PG-E2 at any stage of pregnancy resulted in powerful contraction of the gravid uterus pending preterm labour and birth, (1/). This biosynthesis of PG-E will be reduced or completely blocked by cyclo-oxygenase inhibitors as aspirin and indomethacin, which ultimately resulted in an atonic myometrium as reported in human, sheep and rabbits, (5). Similarly, it was reported that the antipyretic property of paracetamol is the result also of inhibiting prostaglandin synthetase of the brain, (&). Despite the use of aspirin and indomethacin in the management of preterm labour presumably by inhibiting PG-E synthesis yet there was no mention of using paracetamol as a tocolytic.

Salbutamol-albutarol-which is B2 selective adrenergic agonist had been commonly used to suppress preterm labour and to avoid delivery, (1'). This uterine disorder is considered the most challenging obstetric complication encountered by family physician, (9). Although salbutamol is used locally as a tocolytic agent but still carries maternal and perinatal serious risks. Some of the reported side effects associated with the use of salbutamol are maternal acute pulmonary odema, respiratory distress and cardiovasculor disturbances, (I), and neonatal low-sized and cellularity of the thymus and lymph nodes beside a decrease in granulocytes of the peripheral blood, (/0)

Since the analgesic and antipyretic properties are shared by aspirin and paracetamol while the former was used as a cyclo-oxygenase inhibitor of amniotic PG-E2 biosynthesis, and release ( ), so it is presumed that, paracetamol may possess a similar property and could relax the gravid uterus by inhibiting PG-E2.

The search for other tocolytic to substitute salbutamol being effective in delaying human preterm labour and devoided of any side effect has brought up this issue for a longterm strategy and collaboration of investigation.

The initial approach was to examine the relative effects of paracetamol virsus salbutamol in-vitro using resting and ovarectomized rat uterime horns (~/) and then in-vivo on near term gravid rats (12). Their results indicated that, salbutamol and paracetamol relaxed rats uterine horns and delayed delivery beyond term significantly and their newborn litters were large-sized and breathing normally. The justifiable next approach ought to compare their effects on strips of human gravid uterus discarded following hysterectomy.

Material and Methods:

Uniform-sized strips of ruptured

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uterus of gravid women were tested for a relaxing effect after adding acetaminophen and/or s 1butamol into 50 ml capacity inner bath. The hystrectomized patients were multiparai and had enjoyed perinatal period. The patients had no history of toxemia of pregnancy, hypertension nor any associated diseases. The ruptured uteri had occurred because of cephalopelvic disproportion as malpresentation. Strips from the discarded uteri were cut out of the anterior aspect of the upper uterine segment immediately after hysterectomy and placed in preoxygenated bathing medium (Krebs-Henseleit solution) for 18 - 24 hrs at 4°C before use, (13). An initial tension of 2 g was placed on the strip after mounting it, this provided stable and an effective recordings. The bathing medium was warmed up to 38°C and bubbled with air mixture of 5% CO2 and 95% Oxygen. Changes in muscle tension were recorded on SRI kymograph. Pure acetaminophen of Wallace company was dissolved in the bathing medium after vigorous shaking to contain 10mg/ml as a stoke solution. The effect of adding 50 mg of acetaminophen into 50 ml of the inner bath capacity was maintained, that is by taking out 5 ml of the bathing medium before adding 5ml of the stock solution. The effect was compared with the addition of 5 µg salbutamol, that is by taking 0.01 ml of 0.5 mg/ml of ventoline sulphate ampule, of Allen and Hombury Ltd. The bathing medium used was Krebs-Henseleir solution which has the following composition in mM/L:- NaCl, 118; KCI, 4.6; NaHCO3 25; CaCI2 2.5; MgSO4 -7H20; 1.2; KH2PO4 1.2; Glucose, 5.0,

. The effects of acetaminophen and satbulamol were tested on activated strip by the addition of 100 µg of adrenaline, that is by taking 0.05 ml of 2 mg adrenaline / ml of 0.1 N HCI, of ADH Biochemical as well as on resting (inactivated) strip. The reported records of the tensions developed for each test were chosen as the more frequently recorded response out of 16 trials. Furthermore, the relative depressing effects of the activated strip induced by acetaminophen and that by salbutamol were measured in mm of tension. Thus, tension changes of the 16 trials for each test were statistically evaluated and expressed in term of X±SD and the differences were assissed using Chi-square and the ANOVA test.

Results:

Consistent responses observed when the uterine segments were initially stored for 18-24 hrs at 4°C in a preoxygenated bathing medium which was changed twice daily. The addition of 100 pg adrenaline activated the strip by increasing its tension (47.8 + 2.65 mm) which lasted for more than 70 minutes, Fig. 1-A.The addition of 5 pg salbutamol to the activated strip, reduced its tension significantly. (44.9 + 2.68 -* 22.7 + 1.49 mm, P< 0.001), Fig. 1-B, this relaxing effect was nearly obtained when 50 mg of acetaminophen was added to the activated strip,(43.6 + 2.32 ---o. 23.8 + 1.87 mm, P< 0.001), Fig. 1-B, while when 3 successive additions of 50 mg acetaminophen 20 min apart to the activated strip resulted in 3 corresponding drops in tension (57.1 + 2.16 -* 32.8 + 2.61 ---o 3.3 + 0.9 mm) which were significantly different, (P< 0.001), Fig. I.-C. The effect of adding 5 µg salbutamol and then 50 mg acetaminophen 1/2 hr apart was additive in nature and the final tension dropped below resting tension. Fig. 1-D. Finally the previous trial of adding 3 doses of acetaminophen were tested on resting strips that is not activated by adrenaline, 15 min apart resulted in corresponding drops in tension as well, Fig. I - E.

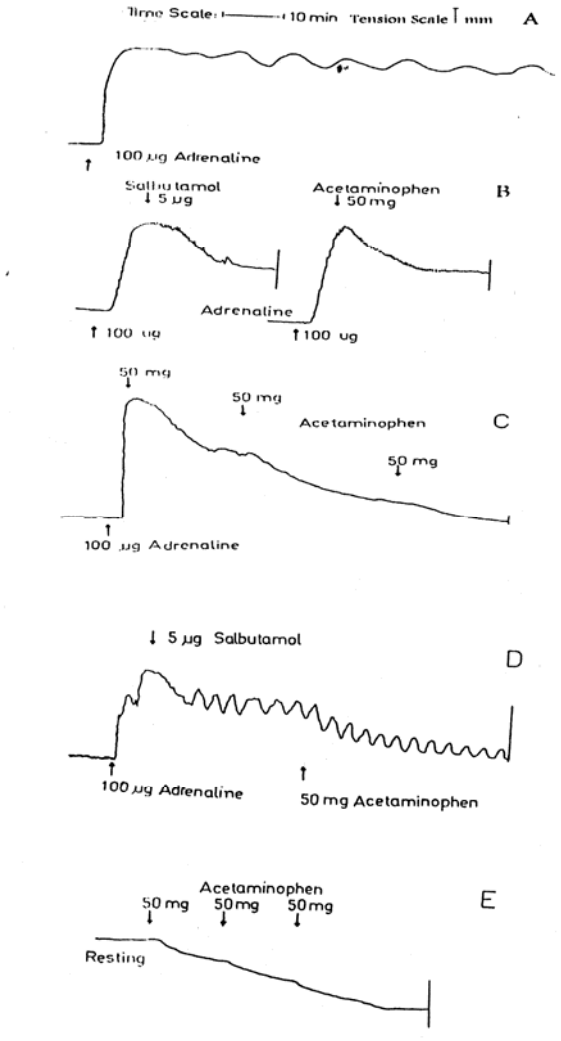

Fig.1 shows changes in tension of resting or initially activated uterine strips by the addition of 100 ug adrenaline .These strips were obtained from ruptured human gravid uterus and mounted in 50 ml of innerbath capacity containing Krebs-Hensliet solution bubbled with 5% CO2 & 95% oxygen air mixture at 38°C and treated with 5 ug salbutamol and/or 50 mg acetaminophen.

Discussion

Since the previously mentioned side effects associated with the use of salbutamol in the management of preterm labour are serious health matters had brought up the issue recently to the world community as a whole for joint research programs.

Atosiban which is an oxytocin antagonist had been well studied in multinational centers world wide with reasonable - sized sample of threatened preterm labour women were given salbutamol and others given atosiban. All women under study were subjected to well planned and critical evaluation of their outcomes. The gathered results collectively revealed that atosiban was effective tocolytic as salbutamol in relaxing the contracted gravid uteri prior to the completion of the 37 t" week of gestation (/1) while their neonatal and maternal outcomes showed no significant differences, (I S). Furthermore, Ampicillin therapy as a tocolytic was also studied and compared with salbutamol and the results indicated that ampicillin had achieved a beneficiary response as well in suppressing preterm labour even in the absence of any infection but the results of their outcomes were inconclusive (16).

These results and others (191,18) revealed that, there is still no acceptable substitute for salbutamol as a tocolytic agent. The present results of uterine strips of gravid women indicated beyond doubt that, the addition of 50 mg acetaminophen or 5 gg salbutamol produced 50% reduction of tension. Early studies on rats (4 /) and currently on human showed that the relaxing effect of acetaminophen addition synergized the effect induced by salbutamol. Because the mode of action of acetaminophen and that of salbutamol are different, this additive effect is of clinical importance since it yield a profound uterine relaxation upon adjunctive use of both drugs and in small doses, This approach will minimize the possible side effects.

It ought to be mentioned that; upon future use of acetaminophen in the management of human preterm labour that, it may induce transient narrowing of the fetal ductal arteriosis and this could lead to pulmonary congestion (//), though the applied dose in rats was 50 mg acetaminophen /Kg body weight daily which appears now relatively very high when applied equivalently to pregnant woman.. Nevertheless, this side effect was not mentioned as such when acetylsolicylic acid or indomethacin were presecribed to retard preterm labour and delivery, (

Future studies on the effectiveness and safety of acetaminophen in the management of preterm laboured women are highly encouraged to settle down the disturbing issue of the neonatal and maternal side effects in term of their nature and severity. Gestation age of the threatened women with abortion should be considered as an additional parameter in evaluating the neonatal outcome. Since the issue of transient narrowing of the fetal ductus arteriosis will recover to normal patency when the treatment takes place at early gestational age and may be critical in advanced age.

Conclusion:

'Experimental research on the feasability of acetoaminophen as another tocolytic instead of salbutamol because mainly of its maternal serious risks and few fetal ones. The search revealed that, acetoaminophen is effective in relaxing the contracting gravid uterine muscle as the case of preterm labour but with quite free maternal side effects as pulmonary oedema, respiratory distress and cardiovascular disturbance while the perinatal may suffer from mild intra-uterine lung congestion as a result of transient narrowing of the ductus arteriosis particularly in advanced gestation age.

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References:

1. Lorejoy, FH. Aspirin and acetaminophen: A Comparative review of their antipyretic and analgesic activity. Pediatr. 1978, 62(suppl): 904-909.

2. 2. Tamaby Raja, RL; Salmon; JA; Karim, SM. Prostaglandins levels in amniotic fluid in preteen labour. Prostaglandins 1977; 13: 339-348.

3. 3. Gyary, G; Kiss, C; Benyo, T. Inhibition of labour by proslaglandins antagonist in impending abortion and preterm labour. Lancet 1974. 9: 293298.

4. 4. Karim, SM; Rao, B. Prostaglandins and Reproduction. Kampala, Ugenda, Lancaster Press, 1975, pp 1-16.

5. 5. Kierse,MJNC Inhibition of prostaglandin synthetase for the treatment of preterm labour In Drife,JO; Calder,AA,(Editors). Prostaglandin and Uterus, London, Springer Verlag,1992.

6. 6. Flower, RJ; Van, JR. Inhibition of prostaglandins synthetase in brain explains the antipyretic activity of paracetamol (4-acetaminophen). Nature (London) , 1972;240:410-411.

7. 7. Gummerus,M;The management of premature labour with salbutamol . Acta Obstet Gynecol Scand 60:375-377 , 1981 .

8. 8. Beverly, A; Von Der Pol. Preterm Labour: Diagnosis and Treatment. American Family Physician, May 15, 1998.

9. 9. Samet, A; Bayoumeu, F; Longrois, D; Laxenaire, Mc. Acute pulmonary oedema associated with the use of B2 mimetic tocolytic agent. Ann Fr Anesth Reanim Jan 2000; 19(1):

35-38.
10. 10. Kaminski,P;Skopinska-Rozewska,E;Wasik,M;Bany,J;Barcz,E;Sommer ,E;Marianoski,L;Thymus and lymph node cell CD4(+) and CD8(+)Marker expression and their angiogenic activity of offspring of salbutamol treated pregnant C3H mice Pharmacol Res. 2000 Jan;41(1):95-99.
11. 11. Khalil, HM; Hilmy, MI. The synergistic effect of paracetamol and salbutamol on rats uterine horms primed with sex hormones. Iraqi J Veterinary Sciences 1995; 8(l): 83-89.
12. 12. Hilmy, MI; Jurna'a HJ; Al-Janabi, G. Maternal and fetal outcome after acetaminophen ingestion during late pregnancy in rats. Iraqi J Veterinary Sciences 1994, 7(2): 71-76.
13. 13. Dusting, GJ; Moncada, S; Vane, JR. Prostaglandins (PGX) is the
14. endogenous metabolite responsible for relaxation of coronary arteries
15. induced by arachidonic acid. Prostaglandins 1977; 13(1): 3-15.
16. 14. Gough,PM.Preterm labour. Obstetric Care 24:2237-2245,1982 .
17. 15. Worldwide Atosiban Versus B Agonist Study Group. The effectiveness and
18. safety of the oxytocin antagonist atosibon versus beta agonist in the
19. treatment of preterm labour. Brit J Obstet Gynecol, 2000 Feb; 108(2): 1333
20. 16. Kenyon, SL; Taylor, DJ; Tarnow-Mordi W. Oracle Collaborative Group. Broad spectrum.antibiotic for spontaneous preterm labour. Lancet 2001 May 31; 357 (9261): 989-994.
21. 17. Csapo, Al; Puri, CP; Tarro, S; Henzl, MRn beactivation of the uterus during normal and premature labour by the calcium antagonist nicardipine. Am J Obstet Gynecol 1982; 142: 483-491.
22. 18. Barclay, L; Magesium sulphate may be harmful in preterm labour. June 26, 2002. Am J Obstet Gynecol 2002; 186: 1111-1118.
23. 19. Souter, D; Harding, J;Mc Cowan,L; O'Donnell, C; McLeay, E; Baxendale,H;Antenatal indomethacin adverse fetal effects confirmed. Aust N Z J Obstet Gynecol. 1998,Fed;38(1):11-16.