# RISK AND BENEFITS: ELECTROLYTES IMBALANCE ASSOCIATED WITH THE USE OF MULTIPLE DRUGS

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**ABSTRACT**

The risk and benefits are of continuous concern following multiple drug administration due to associated adverse drug reactions. In the present study the commonly used drugs for hypertension, diabetes and hyperlipidemia were given to rabbits as individual agents as well as in combination for the period of two months and their effects on electrolytes i.e. sodium, potassium and chloride were noted. Animals received metformin and lisinopril individually revealed highly significant decrease in sodium ($p<0.005$), while chloride was decrease only significantly ($p<0.05$) in animals received metformin, lisinopril and amlodipine as compared to control. Animals received Acarbose, Lisinopril, and Atorvastatin (GlLAt) combination revealed significant increase ($p < 0.05$) in sodium concentration with respect to control. Whereas animal received Glibenclamide, Losartan, Atorvastatin (GLoAt) combination revealed highly significant decrease in potassium concentration ($p< 0.005$).

**KEYWORDS**: Electrolytes, risk and benefit, hypertension, hyperlipidemia and hypoglycemia

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## INTRODUCTION

Several non-prescription drugs are used along with prescription medication that help to improve general health of elderly table 1 (Santoso et al., 2003). Along with these benefits older people are more susceptible to adverse effects of multiple drugs due to several reasons such as reduce metabolism and renal elimination (Dilic et al., 2010).

Hydrophilic drugs are needed to be dissolve in water for but their distribution is reduced due to decrease percentage of water in old age. However, lipid soluble drugs stay for longer period of time as fat contents increases with the age. Renal function decrease in elderly affecting excretion of drugs in urine, hence old people are at high risk of toxic effect for drugs eliminated unchanged in urine. Hence these complications cause drugs to stay for longer period of time in the body of elderly than younger people thus increasing the chances of drug-drug interaction and side effects. It is for this reason medical doctor prescribes doses smaller than usual to old age

patients (Lopez-over Jero et al., 1979, Milsom, Nicholls, 1986; Unger and Gohlke, 1994). Table 2 indicates the toxic effects of some commonly used medicines in elderly patients (Belge et al., 2007; Unger and Gohlke, 1994).

**TABLE: 1**

**Benefits of Common Drugs in Elderly Patients**

(Yasemin et al., 2004)

| Drug | Effect | Benefit |
|---|---|---|
| Vaccines | Prevent infectious diseases | Improve survival of elderly as many have been killed due to viral infection |
| Antibiotics | Pneumonia in old age | Improve survival as Pneumonia may also cause death |
| Antihypertensive | Reduce blood pressure | Benefit to manage strokes and heart attack |
| Antihyperglycemic | Reduce blood sugar level | Help reduce serious adverse effects of hyperglycemia to eye, kidney and other systems. Facilitate normal living in elderly |
| Pain Killers | Control arthritis | Enable older arthritis patients to continue normal function |
| Hypolipidemic agents | Reduce blood cholesterol | Reduce obesity and atherosclerosis |

**TABLE: 2**

**Disadvantages of Common Drugs used chronically**

(Belge et al., 2007)

| Drugs | Effect | Disadvantage in Elderly |
|---|---|---|
| Anxiolytic | Induce sleep | More sleepier and confused due to prolong stay in body |
| Anticholinergic | Control cold and cough (antihistamine) | Relatively high degree of confusion, blurred vision, constipation, dry mouth, light-headedness, difficulty starting and continuing to urinate |
| Digoxin | Heart disorders | Malfunction of kidneys and decrease body water contents increase drug concentration in body resulting in Abnormal rhythm, nausea and vomiting |
| Antihypertensive | Reduce blood pressure | Both effects are greater in degree in elderly patient than young resulting |
| Amitriptyline | Reduce depression | Strong cholinergic effect and marked drowsiness |
| Antihistamine (femotidine) | Heart burn | Confusion |
| NSAIDs | Pain control | Dizziness and confusion |
| Muscle Relaxants | Reduce muscle spasm | Anticholinergic effects, drowsiness and weakness. |

## MATERIAL AND METHODS:

### Sample Collection

Blood samples of 5 ml were collected at the end of dosing period i.e. 60 days from heart through cardiac puncture in siliconised glass tube (Heyns, et al, 1981) and plasma was immediately separated out by centrifugation at 3000 rpm for 15 min to yield platelet poor plasma by Humax 14 K (Germany). Biochemical assays for electrolytes sodium, potassium and chloride was done using separated plasma.

### EFFECT ON ELECTROLYTES

**a) Sodium:** Serum sodium was estimated photometrically by Mg-Uranylacetate, color test method (Trinder, 1951).

**b) Potassium:** Potassium was estimated by photometric turbidimetric test (Hillmann and Beyer, 1967). Potassium ions in a protein-free alkaline medium react with sodium tetraphenylboron to produce a finely dispersed turbid suspension of potassium tetraphenylboron. The turbidity produced is proportional to the potassium concentration and read photometrically.

**c) Chloride:** Chloride was determined photometrically by TPTZ method (Fried, et al., 1972). Chloride ions react with mercury (II) - 2, 4, 6-tri-(2-pyridyl)-s-triazine (TPTZ) complex to form mercury (II)-chloride. The liberated TPTZ reacts with iron (II) ions yielding a blue colored complex. The resulting absorbance change at 590 nm is directly proportional to the amount of chloride ions in the sample.

### STATISTICAL ANALYSIS

All values were compared with control by taking mean and standard error to the mean using two-way analysis of variance (ANOVA) followed by post hoc. Data was reported as mean ± standard error to the mean with 95% confidence interval and p-values were observed. Values of $p<0.05$ were considered as significant and $p<0.005$ as highly significant (Christensen, 2002).

## RESULT:

Table 3 shows the comparison of sodium, chloride and potassium concentrations among control animals and animals kept on individual drugs and their combinations for 60 days in normal therapeutic doses.

Animals received acarbose, glibenclamide, losartan and atorvastatin individually and metformin; amlodipine and atorvastatin (MAAt) in combination did not reveal significant change in sodium, chloride and potassium concentrations at the completion of dosing period.

Animals received metformin and lisinopril individually revealed highly significant decrease in sodium concentration i.e. 42.28±2.80 µg/ml and 38.75 ±6.10 µg/ml respectively as compared to control i.e. 142.6±5.40

µg/ml. However decrease in chloride concentration was significant as compared to control i.e. 84.3±0.34 µg/ml and 73.4±0.24 µg/ml respectively with respect to control i.e. 100.25±0.38 µg/ml. Conversely there was no significant alteration in potassium concentration at the end of dosing interval.

Animals received amlodipine alone revealed highly significant decrease in chloride concentration i.e. 59.98±1.40 µg/ml with respect to control i.e. 100.25±0.38 µg/ml, while there was no significant alteration in concentration of sodium and potassium at the end of dosing.

Animals received Acarbose, Lisinopril, Atorvastatin (GlLAt) combination revealed significant increase in sodium concentration i.e. 168.68±11.00 µg/ml with respect to control i.e. 142.6±5.40 µg/ml. On contrary there was no significant change in concentrations of chloride and potassium at the completion of dosing interval.

Animals received Glibenclamide, Losartan, Atorvastatin (GLoAt) combination revealed highly significant decrease in potassium concentration i.e. 1.41±0.59 µg/ml with respect to control values i.e. 4.18±1.30 µg/ml. Conversely there was no significant change in concentrations of sodium and chloride at the completion of dosing interval.

**TABLE: 3**

**COMPARISON OF ELECTROLYTE LEVELS FOLLOWING 60 DAYS ADMINISTRATION OF INDIVIDUAL DRUGS AND THEIR COMBINATIONS**

| Parameters/ Groups | Sodium | Chloride | Potassium |
|---|---|---|---|
| | (µg/ml) | | |
| Control | 142.6±5.40 | 100.25±0.38 | 4.18±1.30 |
| Acarbose | 133.8±3.40 | 99.1±0.66 | 4.44±0.23 |
| Glibenclamide | 131.7±8.90 | 96.6±0.61 | 4.18±0.91 |
| Metformin | 42.28 ±2.80** | 84.3±0.34* | 7.22±0.33 |
| Lisinopril | 38.75 ±6.10** | 73.4±0.24* | 7.16±0.33 |
| Losartan | 129.55±9.40 | 94.36±0.43 | 4.62±0.52 |
| Atorvastatin | 131.74± 11.0 | 101.03±0.37 | 4.62±0.52 |
| Amlodipine | 145.16±6.12 | 59.98±1.40** | 4.45±0.10 |
| GlLAt | 168.68±11.00* | 119.12±0.14 | 4.11±0.51 |
| GLoAt | 149.50±6.90 | 90.57±0.30 | 1.41±0.59** |
| MAAt | 146.71±7.1 | 88.71±0.32 | 5.50±0.80 |

n=10

Mean ± S.E.M

*p < 0.05 significant with respect to control

**p <0.005 highly significant with respect to control

**DISCUSSION AND CONCLUSION**

In the present study the animal received GLoAt combination showed an insignificant increase in level of sodium with respect to control (Mazzon et al., 2001), which may be due to nephrotoxic effect of losartan and atorvastatin seen in animals received these drugs alone although in combination the microscopic examination of kidney did not revealed any abnormality however, it may be due to blockade of renin-angiotensin system by losartan that plays an important role in regulation of the kidney function.

While the animals received metformin and lisinopril showed highly significant decrease in sodium level, results of present study are supported by previous study since both the drugs decrease serum sodium due to enhanced glomerulus filtration rate (Firas et al., 2009).

Potassium is the major component for cardiac function and abnormality in potassium level may results in cardiac dysfunction, since low potassium is associated with abnormal cardiac rhythm (Ozbek et al., 2000).

In present study no change in potassium levels of any animal group was observed except the animals of group received GLoAt combination which showed highly significant decrease in potassium, this may be due to the nephrotoxic tendency of losartan and atorvastatin at tubular level (del Castillo et al., 1998). The exact reason for the decrease in potassium is not known but it may be due to cumulative administration of losartan and atorvastatin causing decrease potassium due to excessive loss in urine (Mcnally and Feehally 1992).

Chloride maintains osmotic pressure in combination with sodium. An elevated level results due to abnormal kidney function while low levels are associated with diarrhea and vomiting (Patil et al., 2010). In present study significantly low chloride levels were found in animals received metformin, lisinopril this may be due to enhance rate of filtration (Firas et al., 2009). There was highly significant decrease in animals received amlodipine which may be associated with its capability to lower the blood pressure by removing excessive electrolytes including sodium and chloride (Delsing et al., 2003).

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