Acetylsalicylic acid and its derivatives: the dynamics of the circulatory dimensions

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Abstract. The paper presents the research of the acetylsalicylic acid effect and its complex compounds with the metals of cobalt (Co2+), zinc (Zn2+), nickel (Ni2+) and manganese (Mn2+) at the multiple administration in the dose of 10 mg/kg on the indices of the central haemodynamics of the rats (heart rate; arterial pressure). It has been found out that a multifold administration of acetylsalicylic acid and salicylates of cobalt, zinc, nickel and manganese affect the indices of the rats’ central haemodynamics. The obtained data confirm the cardiac efficiency of new coordinating compounds, and have a further studying perspective of their biological effect in chronic experiments.

1. Introduction

Recently considerable achievements in different spheres of medicine have been done due to the introduction of new highly active medications, created on the basis of the known and well-studied medicines [1, 2]. One of them is acetylsalicylic acid (ASA), which as a medication has been used for more than 100 years, and belongs to the group of nonsteroid anti-inflammatory medicine and has a wide range of therapeutic effects (antipyretic, analgetic, anti-inflammatory, anti-aggregate, antioxidant, antidepressant, antimigrainous, anxiolytic, antineoplastic, etc.). Numerous large-scale clinical experiments have shown the ASA efficiency in treating and preventing diseases of cardiovascular system (CVS) [3, 4]. However, along with the proved positive therapeutic effects, ASA, among all the nonsteroid anti-inflammatory medications, is leading not only in the amount of use but also in the total amount of side effects, which also include negative effects on the immune and digestive systems, as well as the skin and hypodermic tissues [5]. The search for new biologically active compounds on the ASA basis has led to the synthesis of its salts and complex compounds, which have been practically used due to the probable enhancement of therapeutical effects of the molecule-predecessor and the decrease of side effects [1, 2].

The non-narcotic analgetics – salicylates of bivalent metals – can become such relatively safe medications [1]. At the Department of Human and Animal Physiology and Biophysics we have done the first researches of biological activity of newly synthesized salicylates of cobalt (ASCo2+), zinc (ASZn2+), nickel (ASNi2+) and manganese (ASMn2+) at a single administration of the doses 5, 10 and 20 mg/kg, which demonstrated their cardioprotective efficiency relative to the indices of the central and peripheral haemodynamics [6, 7]. Along with this, the topical issue is the research of ASA and salicylates of cobalt, zinc, nickel and manganese influence at their multifold administrations in the therapeutical dose (10 mg/kg) on the indices of the rats’ central haemodynamics; this was the objective...
of the given research.

2. Research methods

Sixty male laboratory Wistar rats, weighing 180-200 gr ("FSUE "Nursery of laboratory animals "Rappolovo") and having been placed under quarantine not less than for 14 days, were performed the experiment on. The animals were kept under standard conditions of the vivarium at the temperature of 18–22°C on the bedding «Rexofix MK 2000» (on the basis of ear shanks) with the natural 12-hour day-and-night cycle, with free access to water (State Standard 33215-2014 «The handbook of keeping and nursing laboratory animals. The regulation rules on housing equipment and procedure organization»), and to full-fledged granulated food of State Standard P-50258-92. The rats are characterized by an average motor activity and low emotionality in the “open field” test, the rats comprise the majority in the population, that is why they develop the most typical reaction to the activity of different factors [6], including chemical compounds. All animal studies were carried out in accordance with the principles set out in Directive 2010/63/EC of the European Parliament and of the Council of the European Union of 22.09.2010 on the protection of animals used for scientific purposes.

The synthesis, the research of the composition, structure and properties of the coordinating compounds of the salicylates with cobalt (Co²⁺), zinc (Zn²⁺), nickel (Ni²⁺) and manganese (Mn²⁺) were done at the Department of General and Organic Chemistry of V. I. Vernadsky Crimean Federal University under the supervision of Professor A. N. Gusev (the chemical purity was not less than 98.0%).

For the research the rats were divided into 6 groups (10 rats in each):

Group 1 – control group (C) – the animals which were intraperitoneally injected with the physiological solution (NaCl, 0.9 %), volume 0.2 ml;

Group 2 – the animals which were intraperitoneally injected with the ASA in the dose of 10 mg/kg, volume 0.2 ml;

Group 3 – the animals which were intraperitoneally injected with ASCo²⁺ in the dose of 10 mg/kg, volume 0.2 ml;

Group 4 – the animals which were intraperitoneally injected with ASZn²⁺ in the dose of 10 mg/kg, volume 0.2 ml;

Group 5 – the animals which were intraperitoneally injected with ASNi²⁺ in the dose of 10 mg/kg, volume 0.2 ml;

Group 6 – the animals which were intraperitoneally injected with ASMn²⁺ in the dose of 10 mg/kg, volume 0.2 ml.

The intraperitoneal injections of ASA and its derivatives were done daily during 20 days at the same time of the day (from 8.00 to 11.00). The registration of the researched indices was done on the 1st, 5th, 10th, 15th, and 20th day of the observation 20 minutes later after the injection of the compounds, as at this period their maximum concentration in the blood can be observed.

In the animals of all the groups with the help of the system NIBP200A («Biopac Systems, Inc.», USA) the following characteristics were registered: heart rate (HR, rate per minute); systolic pressure (SP, millimeters of mercury); diastolic pressure (DP, millimeters of mercury); and the sphygmic arterial pressure (SAP, millimeters of mercury; the difference of SP and DP indices) was calculated. In order to do that, the animals were placed into an individual box and were carried into the chamber Biopac with a constantly maintained temperature 33°C for creating comfortable conditions for the animal. The recording of the HR and AP (arterial pressure) was done during 5 minutes after the moment of the stabilization of sensor’s signals; the sensors were put on the proximal end of the rat’s tail. This time was enough for the fivefold measurement of AP; along with this the HR was registered continuously. The recording and processing of the data were done on the computer with the help of the software «Acq Knowledge 4.2 for MP150».

The graphic design and statistic data processing was done with the help of the program Microsoft Excel and software package StatSoft STATISTICA. Non-parametric statistical methods were used, as the distribution of variables’ values differed from the normal one. The credibility of statistical
differences between the control (intraperitoneal injection of the physiological solution) and experimental groups (the administration of ASA and ASCO\textsuperscript{2+}, ASZn\textsuperscript{2+}, ASNi\textsuperscript{2+} and ASMn\textsuperscript{2+}) was defined according to the Mann-Whitney criterion.

To analyze the efficiency of the biological activity of ASA compounds with metal in comparison with the molecule predecessor (ASA) the calculation of the efficiency coefficient (EC) was done according to the formula:

\begin{equation}
EC = (AS_{\text{met.}} - ASA)/ASA,
\end{equation}

where \(AS_{\text{met.}}\) – are the values of the indices registered in the animals at the administration of salicylates \(\text{Co}^{2+}, \text{Zn}^{2+}, \text{Ni}^{2+}, \text{Mn}^{2+}\) (average values of the measurements in each experimental group); \(ASA\) – are the values of the indices registered in the animals at the administration of ASA (average values of the measurements in Experimental group 2).

EC equals nought if the efficiency of the tested compound \(AS_{\text{met.}}\) relative to the registered index corresponds to such for ASA; EC has a positive value if the value of the registered index of the tested compound \(AS_{\text{met.}}\) excels the value of the same one at the administration of ASA; and EC has a negative value if the value of the registered index of the tested compound \(AS_{\text{met.}}\) is less than the value of the given index at the administration of ASA.

3. The results of the research

As the done researches show, in the animals of the control group at a multifold administration of the physiological solution during 20 days of the observation the indices’ values changed in the following range: SP from 106.83 to 112.89 millimeters of mercury, DP from 68.66 to 73.16 millimeters of mercury, SAP from 35.37 to 42.62 millimeters of mercury, HR from 388.55 to 338.04 rates per minute, i.e. in average the indices were: SP 109.22 ±4.84 millimeters of mercury, DP 70.92 ±5.33 millimeters of mercury, SAP 38.29 ±5.67 millimeters of mercury, HR 357.39 ±10.75 rates per minute; this corresponds to the results of our and other experimental researches [6, 8].

The influence of a multifold administration of ASA and its compounds on HR.

After a single administration of ASA there was the decrease of the HR values by 12.61% (\(p \leq 0.001\)) relative to the value of this index in the control animal group (figure 1-a). After fivefold administration of ASA there was an increase of this index values relative to the same, registered on the first day of the observation, however, they remained lower than the same in the control (\(p \leq 0.05\)). It is necessary to mention that after tenfold administration of ASA there was a tendency to the HR increase (\(p \geq 0.05\)), and after fifteenfold ASA administration there was a statistically significant increase of HR values by 9.10 % (\(p \leq 0.001\)) relative to the values of this index in the control animal group (figure 1-a). However, after twentyfold ASA administration the HR were approximate to the same values in the control animal group, this is evident by the absence of statistically significant differences (figure 1-a).

After a single administration of the salicylates \(\text{Co}^{2+}, \text{Zn}^{2+}, \text{Ni}^{2+} \text{ and Mn}^{2+}\), similarly to ASA, there was a decrease of the HR values, mostly expressed after the injection with ACNi\textsuperscript{2+} (by 15.42 %; \(p \leq 0.001\)) relative to the values in the control animal group (figure 1-a), this corresponds to our data of the previous researches [6].

The following day at the administration of ASCO\textsuperscript{2+} into animals there was an increase of HR relative to the same registered on the first day of the observation (figure 1-a). As regards to the values in the animals of the control group, the reliable changes during the whole observation period were not revealed (\(p \geq 0.05\)). Along with this, after fivefold administration of ACCo\textsuperscript{2+} the statistically significant increase of HR by 11.50 % (\(p \leq 0.001\)) was observed relative to the same in the animals injected with ASA; this is evident due to the positive EC values.

The most evinced HR values’ changes were observed in the rats after the administration of ASZn\textsuperscript{2+} relative to the values in the control group as well as in the animals being injected with ASA (figure 1-a). Thus, at the administration of ASZn\textsuperscript{2+} into animals on the 5\textsuperscript{th}, 10\textsuperscript{th} and 15\textsuperscript{th} days of the observation this index increased by 31.58 % (\(p \leq 0.001\)), 44.66% (\(p \leq 0.001\)) and 42.62% (\(p \leq 0.001\)) correspondingly relative to the values in the control group. Along with this, the increase of the HR was in average by
36.48 % (p≤0.001) more evinced than after ASA injection; this is presented by the positive values of the efficiency coefficient. After twentyfold administration of ASZn²⁺ the values of HR approximated to the same ones both in the control group and in the group of rats which were injected with ASA daily; this is evident due to the absence of statistically significant differences.

After fivefold administration of ASNi²⁺ into the animals the HR values increased relative to the values of this index, registered in the rats of this group after a single injection of this compound, and approximated to the control ones (figure 1-a). After ten- and fifteenfold administration of ASNi²⁺ into the animals there was an increase of the HR values by 16.32% (p≤0.001) and 19.05% (p≤0.001) correspondingly relative to the control values of this index and by 12.41% (p≤0.001) and 9.11% (p≤0.001) relative to the same in the animals being injected with ASA (figure 1-a). It is necessary to mention that the HR values approximated to the control ones after twentyfold administration of ACNi²⁺, this is evident due to the absence of statistically significant differences with the index values in Groups 1 and 2 of rats.

After fivefold administration of ASMn²⁺ into animals there was an increase of the values of this index relative to the same, registered on the 1st day of the observation, however they remained lower than of the values in the control (p≥0.05) (figure 1-a). After ten-, fifteen- and twentyfold administration of ASMn²⁺ there was an increase of the HR values by 32.80 % (p≤0.001), 23.73% (p≤0.001) and 15.54% (p≤0.001) correspondingly, as relative to the values in the control group, so and by 28.34% (p≤0.001), 13.40% (p≤0.001) and 10.73% (p≤0.001) relative to the values in the animals being injected with ASA (figure 1-a). It is necessary to pay attention to the fact that only when animals are administered ASMn²⁺, in contrast to other tested compounds, the statistically significant differences of this index were registered on the 20th day of the experiment relative to the values in the animals from Groups 1 and 2.

Thus, onefold administration of ASA and the tested salicylates into the animals led to the HR decrease, i.e. to the development of bradycardia, and the following day of the observation the administration of ASNi²⁺, ASMn²⁺ and particularly of ASZn²⁺ contributed to the HR increase, i.e. to the development of tachycardia, and on the 20th day of the observation the approximation of HR values to the control values level, except for ASMn²⁺, happened.

**The influence of a multifold administration of ASA and its derivatives on the arterial pressure.**

At a multifold administration of ASA into animals statistically significant changes of SP values were not observed relative to this index value in the control animal group (figure 1-b). Along with this after five- and tenfold administration of ASA there was a reliable lowering of DP in average by 12.88 % (p≤0.001) and, as a consequence – the increase of SAP in average by 16.08 % (p≤0.001) relative to the value of this index in the control animal group (figure 1-c). The following day of the observation there was a decrease of DP values relative to the same, registered on the first day of the observation; however, the statistically significant differences with the control were not observed (p≥0.05) (figure 1- b, c).

Similarly, to ASA effect, at one-fold administration of ASCO²⁺ the changes of SP and DP values, relative to this index in the control groups of animals, were not registered (figure 1-B, C). The following day there was a tendency to the decrease of the arterial pressure indices (p≤0.001), however, only after tenfold administration of ASCO²⁺ there was a statistically significant decrease of SP by 10.49 % (p≤0.001), of DP by 14.43 % (p≤0.001) relative to the values of these indices in the control animal group (figure 1- b, c).
Figure 1. Changes in heart rate (a), systolic pressure (b), diastolic pressure (c) with the administration of acetylsalicylic acid (ASA) and salicylates of cobalt (ASC0\(^{2+}\)), zinc (ASZn\(^{2+}\)), nickel (ASN\(^{2+}\)) and manganese (ASMn\(^{2+}\)) relative to the values in the control group, taken as 100% at a different time of the experiment (1, 5, 10, 15, 20 days).

Notes: * - the level of reliability of differences according to the Mann-Whitney criterion relative to the values of indices in the control group; # – the level of confidence of differences according to the Mann-Whitney criterion relative to the values of indices in the group of animals that were administered acetylsalicylic acid (ASA).

After twentyfold administration of ASC0\(^{2+}\) there was an increase of the arterial pressure indices, however, statistically significant differences with the control were not observed (p≥0.05) (figure 1 – b, c). Statistically significant differences between the AP values of the animals, being multifold injected with ASC0\(^{2+}\) and ASA, were not registered at any observation period, this is confirmed by the EC being equal close to the nought.

At one-fold administration of ASZn\(^{2+}\) into animals, in contrast to ASA and other salicylates, there was a statistically significant decrease of the values of SP by 8.38 % (p≤0.001) and an increase of DP values by 12.30 % (p≤0.001) and, as a consequence – an evinced decrease of SAP values by 39.89 % (p≤0.001) relative to the values of the researched indices in the animals from the control group (figure 1 – b, c). After fivefold administration of ASZn\(^{2+}\), on the contrary, there was a SP increase and DP decrease relative to the values, registered on the 1\(^{st}\) day of the experiment, however, statistically significant differences with the control were not observed (p≥0.05). After fifteenfold administration of ASZn\(^{2+}\) there was a statistically significant increase of DP values by 7.06 % (p≤0.001) both relative to the control and by 15.72 % (p≤0.001) relative to the same in the animal, being injected with ASA (figure - c). After twentyfold administration of ASZn\(^{2+}\), the more evinced AP values’ changes happened: an increase of SP by 35.21 % (p≤0.001) and DP by 38.95 % (p≤0.001) correspondingly relative to these values in the control animal group (figure 1 – b, c).

While researching, there were registered definite differences of AP values’ changes at the administration of ASZn\(^{2+}\) and ASA into the rats. Thus, after one-fold administration of ASZn\(^{2+}\) there was a statistically significant increase of DP by 11.07 % (p≤0.001) relative to the same in the animals,
confirmed by the extensive pharmacological studies. It is necessary to point out that after twentyfold administration of ASZn\(^{2+}\) there was an opposite reaction of SP and DP to ASA and ASCO\(^{2+}\). SP and DP increased in the animals of this group and were 135.63 % (p≤0.001) and 139.60 % (p≤0.001) correspondingly relative to the values of this index in the animals, being injected with ASA, this is confirmed by the positive EC.

After multifold administration of ASNi\(^{2+}\) into animals, SP and DP did not differ reliably from the same in the control group of rats, except the 20\(^{th}\) day of the research, when the animals in Group 5 demonstrated the increase of DP values by 9.35% (p≤0.001) relative to the values in the rats under the control (figure 1–b). Along with this there was a statistically significant decrease of DP values by 7.44 % (p≤0.001) after one-fold administration of ASNi\(^{2+}\) and, opposite, an increase of this index values, after five- and tenfold administration of the substance, in average by 13.83% (p≤0.001), and after twentyfold administration there was an increase by 17.73% (p≤0.001) relative to the values in the animals, being injected with ASA (figure 1–c), this is evident by EC at the given observation period.

At one-fold administration of ASMn\(^{2+}\) into animals the values of the SP and DP indices were at the level of the control group values (p≥0.05). However, after five- and tenfold administration of ASMn\(^{2+}\) there was a statistically significant increase of the values of AP indices, both relative to the values in the control group and in the animals being injected with ASA (figure 1-b, c). The following day there was a decrease of SP and DP values to the level of the values in the control group (figure 1–b, c).

Thus, during the research we exposed the effect of ASA and salicylates on the systemic AP of the experimental animals. One-fold administration of ASA and the tested salicylates, except for ASZn\(^{2+}\), did not cause any changes of SP and DP values relative the same in the control group. However, at a daily administration of the researched substances during 20 days the changes were exposed in the indices of AP both relative to the values of the given indices in the control group and in the animals, being injected with ASA, this may demonstrate the cumulative effect and is in agreement with other scientific data [9, 10].

As opposed to the initial compound, the multifold intraperitoneal administration of ASZn\(^{2+}\) and ASMn\(^{2+}\) into rats in a therapeutic dose (10 mg/kg) caused the increase of the systolic and diastolic AP, but in different observation periods; and the administration of ASNi\(^{2+}\) caused only the increase of diastolic AP. Along with this after the twentyfold administration of salicylates the values of both HR (except for ASMn\(^{2+}\)), and of AP (except for ASZn\(^{2+}\)) returned to the initial ones.

It is necessary to point out that the effect of ASA on HR and AP of healthy people was studied in several researches, the results of which either did not show visible effects of the substance on the given indices, or there was found out a dose-dependent decrease of SP and DP [11, 12]. In particular, there was no evident effect of the aspirin (7 capsules of 325 mg during 60 mins) on the HR and AP of healthy people [12]. The authors of the research connect these effects with the ASA property to inhibit prostaglandins. In the experiment of T. Furuno et al. on 11 healthy men (23-39 years old) the effect of aspirin (doses from 81 to 660 mg, every 3 days during 13 days) on the HR was not registered [11]. Along with this the preliminary intake of 81 mg aspirin during cardio loading (the inclination of the head by 60 degrees) improved the indices of the volunteers’ heart rate variability [13].

ASA (0.01 mM/kg, 14 days, intragastrically) did not affect the AP and HR of the Wistar rats [14]. In the model of isoprenaline heart attack of rats, the absence of HR and AP changes under the influence of Zn salicylates (100 mg/kg, prorally, 5 days) was registered [9].

Most researches, evaluating the aspirin influence on AP during hypertension, show that while using aspirin is small doses, aspirin itself does not influence the AP values and does not resist the AP lowering with antihypertensive medicines, but improve their effect [8]. Along with this the experimental research of R. Wu et al. shows that ASA relieves the rats’ hypertension, caused by angiotensine II – there was the lowering of SP in average by 15% (30-35 millimeters of mercury). It is necessary to point out that these effects were evident only at the chronic administration of aspirin (prorally, 12 and 56 days in doses of 100 mg/kg) [15].

Therefore, during our researches the changes of the central haemodynamics (CH) indices happened in significantly less doses of the tested substances; this is quite grounded from the pharmacological and...
clinical points of view at the chronic administration of these substances. It may be connected with the use of complex compounds of ASA with metals, as during the complexing process, there is not only strengthening or weakening of definite effects peculiar to the molecules predecessors, but appearing of new characteristics of the derivative substances.

The change of CH indices under the influence of the salicylates can be the result of the unstriated musculature tone change in the walls of the blood vessels and of the change in the functioning of the blood vessels’ endothelium, this had already been exposed in our and other researches of healthy people and experimental animals [6, 16, 17].

Thus, the obtained data confirm the cardiac efficiency of new coordinating compounds and are promising for further research of their biological activity in chronic experiments.

4. Conclusions

1. A multifold administration of acetylsalicylic acid and salicylates of cobalt, zinc, nickel and manganese in the therapeutic dose of 10 mg/kg influences the indices of the rats’ central haemodynamics (heart rate; arterial pressure).

2. A one-fold administration of acetylsalicylic acid and the tested salicylates led to the lower heart rate, i.e. to the development of bradycardia; and the next day of the observation the administration of ASNi\(^{2+}\), ASMn\(^{2+}\) and especially ASZn\(^{2+}\) contributed to the increase of this index, i.e. to the development of tachycardia. However, on the 20\(^{th}\) day of observation there was an approximation of the heart rate values to the level of the control values, except ASMn\(^{2+}\).

3. A one-fold administration of acetylsalicylic acid and the tested salicylates, except ASZn\(^{2+}\), did not cause the change of the arterial pressure. However, at a daily administration of the tested substances during 20 days, the changes of the arterial pressure parameters were exposed as relative to the values of these indices in the control group, just like in the animals, being injected with acetylsalicylic acid. This seems to demonstrate the cumulative effect of salicylates.

5. References

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