Experimental Aluminum Pathology in Rabbits: Effects of Hydrophilic and Lipophilic Compounds

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Aluminum lactate [Al(lact)₃] (hydrophilic, hydrolytically unstable) and aluminum acetylacetonate [Al(acac)₃] (lipophilic, hydrolytically stable) were tested as potential toxicants to rabbits upon IV administration both as aqueous solutions and as liposome suspensions. Both chemicals behaved as cardiotoxic agents when administered as aqueous solutions, but Al(acac)₃ was at least two orders of magnitude more active than Al(lact)₃. Al(acac)₃, but not Al(lact)₃, caused myocardial infarcts resembling those in humans (with contraction bands) at doses as low as 0.24 mg/kg body weight, as well as a prominent acanthocytosis. Al(lact)₃, when administered as a liposome suspension, was about 300 times more toxic than in aqueous solution, although cardiac damage was not infarctual in character. Both chemical and physical speciation of aluminum(III) thus play an essential role in determining the toxicity of the metal.

Introduction

Aluminum(III) is being actively investigated as a metal relevant to neurological disorders, such as Alzheimer’s disease (1,2), dialysis dementia (3), osteomalacia (4), as well as being investigated for ecotoxicological effects (5). A possible role of aluminum uptake in the pathophysiology of dementia is suggested from recent epidemiological literature (7). However, from a biochemical point of view, the etiological connection between aluminum(III) and such pathologies remains an open question (7).

In spite of toxicological (in vivo and in vitro) (6), enzymological (8), and biochemical (6,9) work over the last decade, information on the reactivity of aluminum(III) with Lewis bases suitable for mimicking possible interaction(s) of the metal with receptor sites of biomolecules is scarce (10,11). Moreover, while considerable information is available on the metallo-organic chemistry of aluminum(III) (12), the aqueous chemistry of the ion in the presence of organic ligands at neutral pH is relatively unexplored. Virtually all biological work, thus, depends on the use of aqueous solutions in which the chemical identity (the speciation) of the employed toxin is rather ill-defined. Three main types of aqueous aluminum have been used so far: a) salts of strong acids (e.g., chloride and sulfate); b) salts of moderately strong acid with appreciable metal bonding ability (e.g., lactate and tartrate); and c) hydrolytically stable neutral complexes, i.e., aluminum acetylacetonate [Al(acac)₃] (acetylacetonate=2,4-pentane-dionate) and aluminum maltolate [Al(malt)₃] (maltolate=3-hydroxy-2-methyl-4-pyronate).

Solutions of type a, once adjusted to pH 7.5, produce quantitatively Al(OH)₃ (solubility equal to about 10⁻⁷ M). Among solutions of type b, those obtained from aluminum lactate appear to be stable at pH 7.5, but they are, in fact, probably metastable (13). In this case, the actual identity of biologically active species is a matter of speculation (10). Solutions of type c are currently in use in our laboratory and in other laboratories (1,14); preliminary results obtained with Al(acac)₃ (14) seem to indicate novel biological effects of this metal.

We report here on the first extensive toxicological work carried out with aluminum(III) solutions in which the nature of the administered toxin is either well known, i.e., Al(acac)₃, or at least can be reasonably proposed on the basis of preliminary new findings (15), i.e., aluminum lactate [Al(lact)₃] (lactate=2-hydroxy-propanoate). Data referring to the use of liposomes as carriers of both Al(acac)₃ and Al(lact)₃ are also reported.
Materials and Methods

Animals and Chemicals

New Zealand white adult rabbits were obtained from Morini (Modena, Italy). Animals were maintained at controlled temperature and humidity and were supplied with water and standard rabbit food (Italiana Mangimi, Milano, Italy) ad libitum. The animals were anesthetized with Ketalar (Parke Davis) before being killed.

Al(lact)₃, (Fluka) and DL-dipalmitoylphosphatidylcholine (DPPC) (Sigma) were of reagent grade and used without further purification. Al(acac)₃ was prepared according to Yung and Reynolds (16) and was recrystallized from benzene/light petroleum. The purity of Al(lact)₃ and Al(acac)₃ was checked by elemental analysis. Al(acac)₃ was further controlled by ¹H-NMR and IR spectrometry. Acetylacetone (2,4-pentanedione) (Janssen) was distilled before use. Ultra-pure water was prepared by distillation in a fused silica sub-boiling still and stored in polyethylene bottles. Reagent-grade concentrated nitric acid (Prolabo) was distilled in a sub-boiling still and stored in polytetrafluoroethylene (PTFE) bottles. Diluted nitric acid (1 M) was prepared by weight in a PTFE bottle.

Preparation and Analysis of Liposome Suspensions of Al(lact)₃

DPPC, 15 mg, and 105 mg of Al(acac)₃ (about 0.32 mmole) were dissolved in 2.1 mL of ethanol (95%) at 70°C with stirring. The resulting solution was slowly injected by means of a 50-μL microsyringe into a sterile NaCl solution (9 g/L, 30 mL) at 55 to 60°C. Each 50-μL portion was injected in 10 to 15 sec; during injections, the solution was stirred and the syringe needle was kept about 1 cm below the surface. The solution was allowed to cool under stirring and excess DPPC and Al(acac)₃ were removed by dialysis (cellulose membrane, φ = 1 cm, average pore diameter = 24 Å, exclusion limit 8000 to 15000 D, three treatments with 250 mL of physiological solution for 12 hr at 5°C). The final pH was about 7.0; the product had an opalescent appearance and was stored at 5°C in glass vials. Monolayer and single compartment characteristics of the liposomes were checked by a turbidimetric method (17) and confirmed by electron transmission microscopy (18). The liposomes were found to be stable for about 1 month (turbidimetric test) (17).

The total aluminum content of the liposome suspensions was determined as follows: 0.5 mL of the suspension plus 1.0 mL of water were acidified with 0.2 mL of concentrated HNO₃, and kept at 80°C for 1 hr. The pH was adjusted at 7.4 by addition of 0.6 mL of aqueous NH₃ (25% w/w) and of 5 mL of borate buffer (0.18 M boracic acid, 5 mM sodium tetraborate, pH 7.4). Aluminum was then determined spectrophotometrically as the 8-hydroxyquinolinate complex after extraction with toluene (19).

The aluminum content of the liposomes was determined as follows: 0.5 mL aliquots of the suspension were centrifuged (15 min at 30,000 rpm) to remove the aqueous phase, and the organic residual was treated with 1.5 mL of water and 0.2 mL of concentrated HNO₃; the resulting solution was analyzed as described above. The aluminum content of the liposomes was found to be about 50% of the total.

Preparation and Analysis of Liposome Suspensions of Al(lact)₃

The procedure and molar amounts were the same as for Al(acac)₃, with the exception that Al(lact)₃ was dissolved in the physiological solution to give a 0.05 M concentration; the alcoholic solution contained only DPPC.

As most of the aluminum was expected to be in the external aqueous phase, the dialysis procedure was modified as follows. During dialysis, the external solution was continuously renewed by a peristaltic pump operating at about 35 mL/hr; the external solution was sampled at various times; and its aluminum content determined by ionic chromatography. A bell-shaped concentration versus time profile was obtained, with the aluminum concentration dropping to negligible values (0.4–0.5 μM) after 5 days. The total aluminum content of the dialyzed suspensions was determined as described above; in view of the exhaustive nature of the dialysis procedure, the administered aluminum was assumed to be essentially all liposomes associated.

Administration Protocol, Chemoclinical Analyses, and Autoptical and Histological Evaluation

Animals were injected IV from the rostral auricular vein under sterile conditions. Solutions of Al(lact)₃ and Al(acac)₃ were sterilized by autoclaving at 110°C for 15 min. Control experiments were performed on three rabbits by injection of comparable amounts of free acetylacetone (aqueous solution, 300 μg/day for 16 days).

Urea, glucose, creatinine, total cholesterol, total bilirubin, alanine aminotransferase (ALAT/ GPT), aspartate aminotransferase (ASAT/GOT), alkaline phosphatase, gamma-glutamyltransferase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), total protein, and triglycerides were determined by means of Boehringer kits.

A thorough autoptical examination was performed on most animals. All macroscopic lesions were noted and samples of brain, spinal cord, heart, lungs, liver, spleen, kidneys, and skeletal muscle were examined microscopically after 24 to 48 hr fixation in 10% buffered formalin. Sections were stained with hematoxylin-eosin; brain and spinal cord were also examined with Bodian’s stain; heart was examined with the Alcian-PAS and van Gieson methods.

Decontamination of Analytical Equipment

All the vessels employed for aluminum determination in tissues were decontaminated by washing with a detergent and then with diluted nitric acid and were kept immersed in diluted nitric acid. Fused silica test tubes were boiled in concentrated nitric acid for 1 hr. All the above items were carefully rinsed with ultrapure water before use and allowed to dry in a dust-protected box. Micropipette tips were decon-
taminated before use by loading twice with concentrated nitric acid and then with water.

**Aluminum Determination in Tissues**

Organs removed during the autopic examination were stored at \(-20^\circ C\) in decontaminated polystyrene vessels. A weighed tissue portion (2-5 g) was homogenized in a homemade PTFE potter (10 mL capacity) with 1 to 2 mL of water. The homogenate was then transferred to a decontaminated polypropylene test tube, freeze-dried, and stored at room temperature. The samples were dry ashed according to the following procedure (20): 150 to 300 mg of lyophilized material was directly weighed into a decontaminated 5-mL fused silica test tube and heated in a muffle furnace (temperature program: 1.5 hr each at 100, 150, 200, and 250°C; overnight at 480°C). After cooling, 1 mL of 1 M nitric acid was added, and the test tube was heated at approximately 100°C for 30 min. Occasionally, after this treatment, samples were found to contain small amounts of carbonaceous residue; in this case, the samples were treated in an ultrasonic bath for 1 hr and heated again as above. The samples were finally diluted with 1 mL of water and centrifuged. Aluminum was determined in the resulting clear solution by ion chromatography with colorimetric detection (Fig. 1), using the operating conditions shown in Table 1.

**Results and Discussion**

**Chemical Nature of Al(lact)_3 and Al(acac)_3 in Water**

Aluminum lactate has been frequently employed in toxicological research to prepare stock solutions of Al^{3+} ions. In

![Figure 1](image_url) Detection system employed in the determination of aluminum by ion chromatography. (1) Effluent from the analytical column; (2) buffer; (3) chromogenic agent; (4) peristaltic pump; (5) damper; (6) reactor coil; (7) colorimetric detector.

**Table 1. Experimental details in the determination of aluminum by ion chromatography.**

| Component          | Description                                                                 |
|--------------------|-----------------------------------------------------------------------------|
| Eluent             | 0.15 M ammonium sulfate + 0.30 M ammonium nitrate + 0.10 M nitric acid; flow rate 0.70 mL/min |
| Chromogenic reagent| 2 mM pyrocatechol violet + 8.8 mM nitric acid; flow rate 0.35 mL/min         |
| Buffer             | 3.2 M hexamethylenetetramine + 44.0 mM nitric acid; flow rate 0.35 mL/min    |
| Sampling loop volume | 50 μL                                                                            |
| Detector wavelength | 570 nm                                                                           |

fact, this compound is reported to be "freely soluble in water" (21) and, unlike simple inorganic salts of Al^{III}, does not give rise to aluminum hydroxide precipitation upon neutralization and dilution. This observation is in contradiction with thermodynamic expectations based on a recent potentiometric investigation of the Al^{III}/H_2O/lact- system (19). In the pH range 3 to 5, the species [Al(lact)H_2O]^{12+}, [Al(lact)H(OH)(H_2O)] and [Al(lact)_3] have been identified; the relevant stability constants clearly indicate that at physiological pH values, the total concentration of Al^{III} in equilibrium with solid Al(OH)_3 is unaffected by the presence of lactate.

The apparent contradiction between thermodynamic prediction and experimental fact can be explained either by the existence, at pH 7, of other, yet unknown, coordination compounds under equilibrium conditions, or on the operation of kinetic factors. This latter kind of behavior is not unexpected for Al^{III} complexes under nonacidic conditions (12). Indeed, no aluminum-lactate complexes exist in appreciable amount at pH 7.5; rather, the predominant species are aquo-hydroxo aluminum species, metastable toward Al(OH)_3 formation (15). Based on available thermodynamic data (22), aqueous solutions of Al(acac)_3 should be stable at the concentration levels employed in this work. This was confirmed by the stability with time of the electronic spectra of the solutions.

**Toxicity Data**

A comparison of toxicity between aluminum lactate in aqueous solution (Al(lact),aq) and the same chemical carried by liposomes (Al(lact),lip) revealed that the latter is strongly (at least 300 times) more cardiotoxic than the former (Tables 2 and 3). For example, the data for animals 30 and 31 (Al(lact),lip) and 18 and 19 (Al(lact),aq) show that similar CK figures were reached with analytical amounts of administered toxin that differ by about two orders of magnitude. This prominent enhancement of toxicity for Al^{III} carried by the liposomes in their internal water micropools can be attributed to a biophysical speciation effect.

A liposome-based administration (likely to offer a more bioavailable form of Al^{III}) allows for discrimination between specific cardiotoxic effects of the metal and the rather nonspecific ones caused by the same species at far greater concentrations to brain, liver, kidneys, and lungs (Table 2). In particular, such effects appear to be prominent at Al(lact), does greater than 70 mg/kg body weight. Under these conditions, such massive effects could have led to secondary myocardial damage (e.g., edema).

The biological effect of Al(acac),aq, estimated in terms of cardiotoxicity (Table 4), was also much higher (about 100 times) than that exhibited by Al(lact),aq, but the type of cardiac damage was quite different. Al(acac),aq, produced a myocardial effect, with myocardial necrosis (infarct), prominent contraction bands, and multifocal myocarditis (the protonated free ligand, acetylaceetone, is nontoxic). A 4- to 5-fold increase of aluminum concentration in the cardiac tissue paralleled the histopathological and chemoclinical data. Details of this experimentally induced pathology have been
Table 2. Effects of Al(lact)₃ (aqueous solution). *

| Rabbit no. | Total amount of Al, mg | Time of death | Histopathological findings | Chemoclinical data |
|------------|------------------------|---------------|----------------------------|-------------------|
| 9          | 139 (10 d, 7 i)        | 30 (killed)   | Brain: no lesions          | ND                |
|            |                        |               | Heart: dilated ventricles; focal round-cell inflammation | Cortex: 2.2       |
|            |                        |               | Liver: focal round-cell and leukocytes (eosinophils) inflammatory infiltrate in lobular and portal tracts | Cerebellum: 4.2   |
|            |                        |               | Kidneys: interstitial nephritis | Thalamo-mesencephalon: 1:1 |
|            |                        |               | Lungs: acute stasis        | Liver: 82         |
| 13         | 240 (15 d, 12 i)       | 0             | Heart: massive dilatation, particularly of the right ventricle; interstitial edema and myocardial fiber disarray | Kidneys: 20       |
|            |                        |               | Liver: massive centrilobular necrosis with megakaryocytes and erythroblasts | Heart: 9.2        |
|            |                        |               | Kidneys: severe glomerulopathy with fibrin and basophilic granular material in capillaries; tubular necrosis; extramedullary hematopoeisis |             |
| 14         | 350 (10 d, 5 i)        | 0             | Brain: no lesions          | ND                |
| 16         | 328 (7 d, 4 i)         | 0             | Heart and liver: as for rabbit no. 13 | ND                |
| 18         | 130 (30 d, 21 i)       | 2 (killed)    | Brain and heart: as for rabbit no. 9 | CK⁴: increase up to 530–890 U.I.; other indexes normal |
| 19         | 88 (15 d, 11 i)        | 2 (killed)    |                              | ND                |

* pH adjusted to 7.5 with NaOH; injected volumes: from 0.5 to 2 mL of −0.5 M solution.

Numbers refer to pound registry.

Number of days of treatment (d) and number of injections (i) in parentheses.

Number of days after the last injection.

Average Al concentration, ppm, in controls: total brain, 0.31 ± 0.1; cortex, 0.16 ± 0.03; cerebellum, 0.32 ± 0.12; thalamo-mesencephalon, 0.29 ± 0.14; heart, 0.61 ± 0.26; liver, 0.26 ± 0.03; kidney, 0.54 ± 0.25.

ND, not determined.

CK, creatine kinase. Normal CK value: 330 ± 76 U.I. (23).

Table 3. Effects of Al(lact)₃ (liposome suspension). *

| Rabbit no. | Total amount of Al, mg | Time of death | Histopathological findings | Chemoclinical data |
|------------|------------------------|---------------|----------------------------|-------------------|
| 30         | 0.27 (50 d, 42 i)      | 2 (killed)    | Heart: interstitial hyperplasia and fibroblastic proliferation | CK*: gradual increase up to 1000 U.I. at the end of treatment |
|            |                        |               | Brain, liver, kidneys, spleen, lungs and skeletal muscles: no lesions | As for rabbit no. 30 |
| 31         | 0.02 (7 d, 4 i)        | 2 (killed)    | Heart, brain, liver, kidneys, spleen, lungs, and skeletal muscles: as for rabbit no. 30 |                      |
|            |                        |               | Spinal cord: large infarction of the lumbar tract, probably from ischemic damage |                      |
| 34         | 0.07 (15 d, 11 i)      | 2 (killed)    | Heart, liver, kidneys, lungs, and skeletal muscles: as for rabbit no. 30 | CK and LDH: slight irregular increase |

* pH 7 (spontaneously reached after dialysis); injected volumes: 4 mL of a ~ 0.06 mM suspension.

Numbers refer to pound registry.

Total amount, including aqueous and liposome carried AlⅢ (see text). Number of days of treatment (d) and number of injections (i) in parentheses.

Number of days after the last injection.

CK, pyruvate kinase; LDH, lactate dehydrogenase.

reported (14). It is worth noting that skeletal muscles undergo only indirect (secondary) damages.

The quite different biological effects on the same organ observed in the two cases clearly points to the importance of the speciation (i.e., the nature of the coordination sphere) of the administered metal. Cardiac muscle appears to be a target organ for aluminum (under pathologic conditions) for uremic patients (3). It is apparent that the chemical properties acquired by aluminum(III) in its peculiar speciation as Al(acac)₃ (hydrolytic stability, resistance to scavenging,
Table 4. Effects of Al(acac)₃ (aqueous solution). *

| Rabbit no. | Total amount of Al, mg | Time of death | Histopathological findings | Chemoclinical data | Al concentration in tissues, ppm |
|------------|-----------------------|--------------|----------------------------|-------------------|-------------------------------|
| 26         | 0.8 (13 d, 8 i)       | 0            | Brain: no lesions Heart: dilatation, particularly of the right ventricle; multifocal degeneration of myocardial fibers, with myocardiolysis and contraction bands; interstitial edema and inflammation Liver: massive stasis, with centriflobular necrosis Kidneys: stasis; some eosinophils in glomerular capillaries Lungs: acute stasis and edema Skeletal muscles: no lesions | CK: regular increase up to 1650 U.I. (after eight injections) LDH: slight and irregular increase | ND* |
| 27         | 0.7 (13 d, 7 i)       | 0            | As for rabbit no. 26 | As for rabbit no. 26 | ND |
| 35         | 0.7 (20 d, 15 i)      | 0            | As for rabbit no. 26 | CK: irregular increase up to ~1000 U.I. after each injection LDH: slight and irregular decrease | For rabbit no. 35 |
| 36         | 0.7 (20 d, 15 i)      | 2            | As for rabbit no. 26 | As for rabbit no. 35 | Brain: 0.6 Heart: 2.1 Liver: 2.2 Kidney: 1.0 Cortex: 0.08 Cerebellum: 0.79 Thalamo-mesencephalon: 0.18 Heart: 1.3 Liver: 1.9 Kidney: 1.0 Cortex: 0.28 Cerebellum: 0.26 Thalamo-mesencephalon: 0.33 Heart: 1.45 Liver: 2.4 Kidney: 1.1 |
| 37         | 0.7 (20 d, 15 i)      | 0            | As for rabbit no. 26 | As for rabbit no. 35 | ND |
| 38         | 0.7 (20 d, 15 i)      | 1 (killed)   | Brain, heart, liver, kidneys as for rabbit no. 26 | As for rabbit no. 35 | ND |
| 39         | 0.7 (20 d, 15 i)      | 50           | Brain: no lesions Heart: focal fibrous scars, with some calcified cells Blood: development of acanthocytes | CK: as for rabbit no. 35; gradual return to the normal figure upon stopping the treatment LDH: as for rabbit no. 35; gradual return to the normal figure upon stopping the treatment | Cortex: ~0.08 Cerebellum: 0.44 Thalamo-mesencephalon: 0.16 Heart: 1.8 Liver: 2.6 Kidney: 0.53 |
| 40         | 0.7 (20 d, 15 i)      | 20           | Brain, heart, and blood as for rabbit no. 39 | As for rabbit no. 39 | ND |

* pH 7; injected volumes from 0.5 to 1.5 mL of a ~2.5 mM Al(acac)₃ solution.
* Numbers refer to pound registry.
* Number of days of treatment (d) and number of injections (i) in parentheses.
* Average Al concentration, ppm, in controls: total brain, 0.31 ± 0.1; cortex, 0.16 ± 0.03; cerebellum, 0.32 ± 0.12; thalamo-mesencephalon, 0.29 ± 0.14; heart, 0.61 ± 0.26; liver, 0.26 ± 0.03; kidney, 0.54 ± 0.25.
* CK, creatine kinase; LDH, lactate dehydrogenase.
* ND, not determined.
* Normal CK value: 330 ± 76 U.I. (23).

and lipophilicity) (24) facilitate the action of this artificial toxin not only in reaching the organ, but also in interfering with receptor(s) that are essential to myocardial cell function (M).

The similarity of the cardiotoxic effect of Al(acac)₃lipos and Al(acac)₃lipol (Table 5) might seem surprising, in that a possible synergic action of the lipophilic vehicle with the lipophilic character of the coordination sphere could have been expected. Evidently, the above-mentioned properties of Al(acac)₃ make this complex sufficiently well suited in itself for selectively producing an infarctual cardiac lesion, such that the liposomal vehicle does not provide a significant synergic contribution. The appreciable accumulation of
Table 5. Effects of Al(acac)$_3$ (liposome suspension).*

| Rabbit no. | Total amount of Al, mg* | Time of death* | Histopathological findings | Chemoclinical data |
|------------|-------------------------|----------------|---------------------------|--------------------|
| 5-8        | 0.8                     | 0              | Heart: dilatation, particularly of the right ventricle; multifocal myocytolysis; interstitial edema and inflammation | ND* |
|            | (10-15 d, 7-10 i)       |                | Liver: stasis and mild steatosis Kidneys: stasis; some eosinophils in glomerular capillaries Spleen: congestion | |
| 22         | 0.6                     | 2 (killed)     | As for rabbits nos. 5-8 | CK*: 2-fold increase LDH: 3-fold increase at the end of treatment |
| 23         | 0.6                     | 2 (killed)     | As for rabbits nos. 5-8 | CK: 10-fold increase LDH: 5-fold increase at the end of treatment |

*pH 7; injected volumes from 0.5 to 1.5 mL of a ~3 mM Al(acac)$_3$.
*Total amount injected, including aqueous and liposome carried Al$^{3+}$ (see text). Number of days of treatment (d) and number of injections (i) in parentheses.
*Number of days after the last injection.
*ND, not determined.
*CK, creatine kinase; LDH, lactate dehydrogenase.

铝在肝和肾（表2和4）中的存在是不令人惊讶的，因为这些器官具有特定的解毒功能。

表4的检查表明，实验动物39在20天的治疗方法后存活，共39只。在确认了Al(acac)$_3$对假性心肌梗死的不可逆性后，根据文献(14)，动物被监测了50天。虽然CK和LDH指数返回了正常值，但在3天后，组织病理学分析揭示了心肌梗死区域中胶原蛋白丰富的疤痕组织的替代。组织学检查显示，14天后，动物的死亡是自发性的。

有趣的是，从动物39和40中取出的血样中，显微镜观察显示，细胞核和细胞膜的异常，特别是在脊髓损伤后7天。这些异常表明治疗后出现了显著的形态异常，表现为红细胞的镰刀形溶血(图3)。这一异常可能与血红蛋白在细胞膜上的结构异常(27)相关，或者与Al$^{3+}$的直接作用有关。这些结果支持了另一种理论假设。

如图3所示，红细胞在体外的观察表明，这种毒素在体内可能在没有显著的组织损伤的情况下被有效地解毒，但这种解毒方式并未在体外验证。尽管在体外没有显著的细胞毒性，但铝在体内的分布和影响仍值得进一步研究。

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铝在肝和肾（表2和4）中的存在是不令人惊讶的，因为这些器官具有特定的解毒功能。
No neurological effects were observed with Al(acac)$_3$.

In general terms, the data reported here do not seem to indicate any connection between the IV injection of hydrolytically stable (lipophilic) Al(acac)$_3$ or of hydrolytically (meta)stable (hydrophilic) Al(lact)$_3$ and neurological disorders. The apparent contrast between our results and the neurological disorders with neurofibrilament degeneration observed upon SC administration of Al(lact)$_3$ (28–30) may simply be the result of different administration protocols. In the case of Al(acac)$_3$, the lack of effect may be due to the relatively short treatment times employed so far, together with an overwhelming cardiotoxic activity of the drug. It is possible that much lower doses and prolonged treatment times will lead to the production of neurologic effects.

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