# The SECAR study: Sodium selenite reverses chemotherapy resistance

- After a monotherapy with high-dose sodium selenite, therapy-resistant tumors once again respond to chemotherapy
- High-dose sodium selenite stabilizes more than a third of the patients with therapy-resistant, advanced tumors

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# Therapy-resistant tumors respond again to chemotherapy after monotherapy with high-dose sodium selenite

Meanwhile, high-dose sodium selenite has established itself in cancer therapy as an additive and adjunctive medication (e.g. selenase®). Nevertheless, questions still remain concerning the toxicity of dosages from 1,000 to 2,000 µg per day.

The SECAR study conducted by the renowned Karolinska Institute in Sweden could rebut these misgivings in a dose-escalating clinical trial with sodium selenite using dosages of up to 18,500 µg selenium as sodium selenite. [1]

Moreover, this study pursued a new approach to the use of sodium selenite for cancer patients. Very high-dose sodium selenite was not employed as an additive cancer therapy, but as the sole chemotherapeutic agent for patients with therapy-resistant, advanced tumors. The results of the SECAR study are very promising. After two weeks of high-dose sodium selenite, in the majority of patients the previously resistant tumor once again responded to chemotherapy. Moreover, a regression of the tumor was shown for certain types of cancer.

Additional studies are planned and will deliver detailed data on these very promising results.

## Topic of study

With the SECAR study, the authors wanted to answer the following questions about the effect of sodium selenite on cancer:

1. Does sodium selenite have a direct anti-tumoral effect?
2. Can sodium selenite reverse chemo-resistance?
3. Can sodium selenite alleviate the toxic effects of chemotherapy?

In order to be able to answer these questions, all patients included in the study were treated with the identical chemotherapy after treatment with sodium selenite. It was therefore possible to compare the toxicity and primary anti-tumoral effect before and after the sodium selenite therapy.

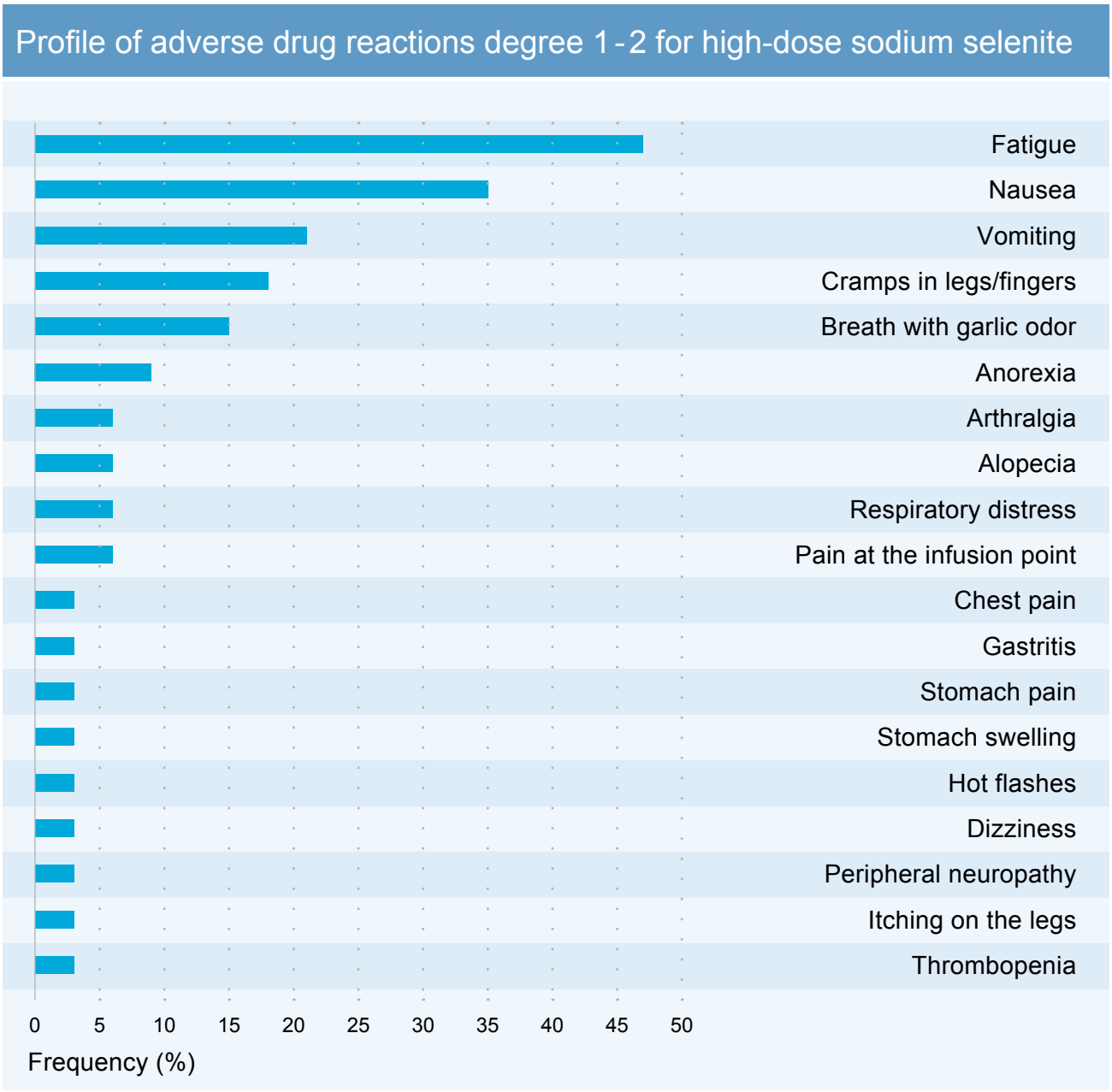
Profile of adverse drug reactions degree 1 - 2 for high-dose sodium selenite
Fatigue
Nausea
Vomiting
Cramps in legs/fingers
Breath with garlic odor
Anorexia
Arthralgia
Alopecia
Respiratory distress
Pain at the infusion point
Chest pain
Gastritis
Stomach pain
Stomach swelling
Hot flashes
Dizziness
Peripheral neuropathy
Itching on the legs
Thrombopenia
0
5
10
15
20
25
30
35
40
45
50
Frequency (%)

*Fig. 1*

## Study design

The SECAR study was an open-label dose-escalating phase I clinical trial with intravenously administered sodium selenite as the single active ingredient.[1] The study included 34 patients with various therapy-resistant tumors. It primarily dealt with lung cancer (71 %). The second most common type of tumors were colon cancer (12 %).

Groups of three patients were formed for the dose-escalating study. This group received the same dose of sodium selenite during the entire treatment. If the patients showed no dose-limiting toxicity symptoms, then the dose was increased. Dose-limiting toxicity for 0/3 or 1/6 of the patients were defined as maximum tolerated dose.

The primary endpoint of the study was safety, the dose-limiting toxic effects, and the maximum tolerated dose of sodium selenite. A secondary endpoint was the evaluation of the primary response to sodium selenite.

## The maximum tolerated dose of sodium selenite: 10,2 mg/m²

Almost no symptoms occurred in doses lower than 3.0 mg/m² selenium. The most common adverse reactions were fatigue, nausea and vomiting *(Fig. 1)*. These side effects occurred starting from doses of 4.5 mg/m². Adverse reactions greater than degree 3 occurred only for doses greater than 12.8 mg/m² *(Fig. 2)*. For a dose ≤ 10.2 mg/m², no dose-limiting toxicity occurred. Dose-limiting toxicities of sodium selenite were acute, of short duration and reversible within 1 - 2 days. Diverse biological markers of the organ functions showed no critical systemic toxicity. The authors conclude that a dosage of ≤ 10.2 mg/m² selenium per day for 2 weeks is safe and tolerable. For doses of 10.2 mg/m² selenium and above, betamethasone and omeprazole were routinely administered as a pretreatment to counteract the most frequent adverse reactions.

## How is the specification mg/m² converted to µg?

The surface (m²) is calculated as follows:

$$\sqrt{\text{height [cm]} \times \text{weight [kg]} / 3600}$$

An average patient with 170 cm and 70 kg has a surface area of 1.82 m². The maximum tolerable dose of 10.2 mg/m² selenium per day yields a daily dose of 18.56 mg or 18,564 µg. The dose of 3.0 mg/m² selenium, when almost no symptoms appeared, corresponds to a daily dose of 5,460 µg selenium *(Fig. 3)*.

1,000 to 2,000 µg selenium in the form of sodium selenite is therefore safe and generally not associated with adverse reactions.

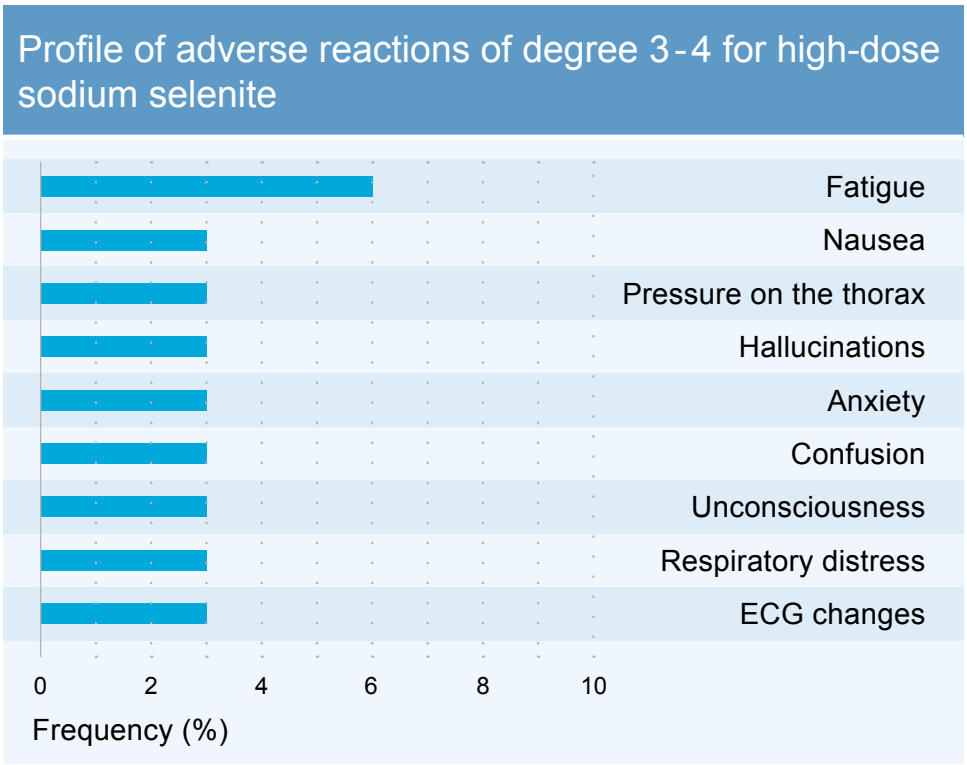
Profile of adverse reactions of degree 3-4 for high-dose sodium selenite
Fatigue
Nausea
Pressure on the thorax
Hallucinations
Anxiety
Confusion
Unconsciousness
Respiratory distress
ECG changes
0
2
4
6
8
10
Frequency (%)

*Fig. 2*

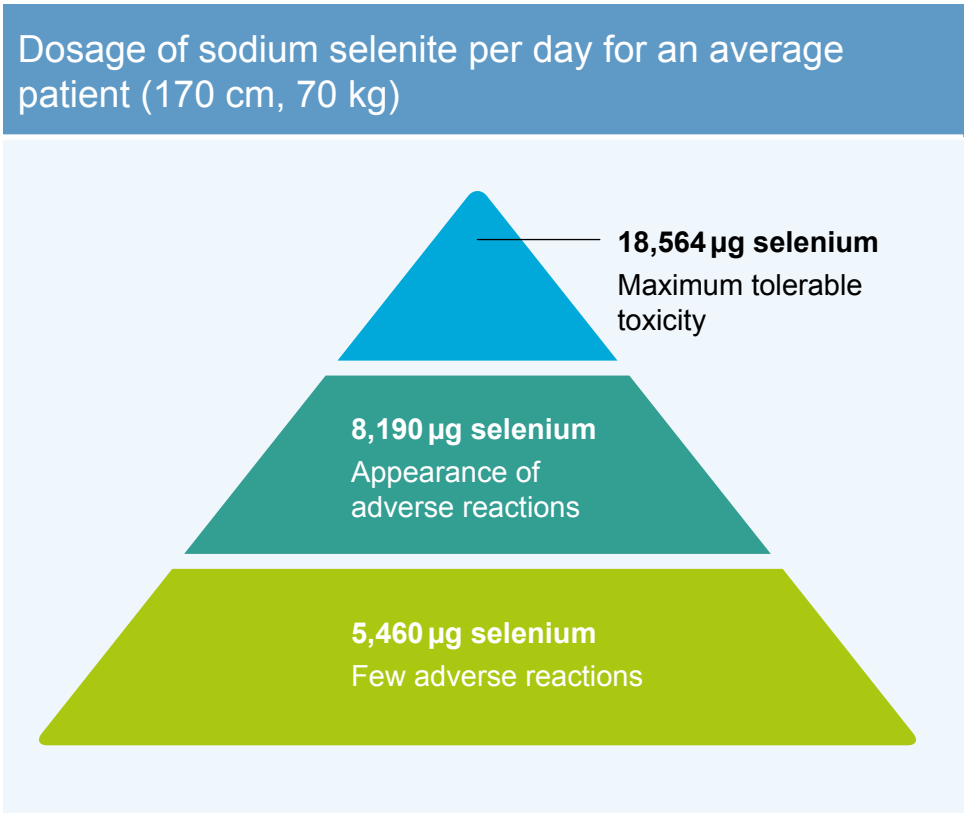
Dosage of sodium selenite per day for an average patient (170 cm, 70 kg)
18,564 µg selenium
Maximum tolerable toxicity
8,190 µg selenium
Appearance of adverse reactions
5,460 µg selenium
Few adverse reactions

*Fig. 3*

### Plasma selenium concentration for high-dose sodium selenite therapy

The plasma selenium concentration was measured on day 1, 5, 8 and 12 of the therapy with sodium selenite, before and after the infusion *(Fig. 4)*. A close correlation was revealed between actual and calculated plasma selenium concentration. The maximum plasma selenium concentration increased linearly with the total selenium dose during the entire study. The median plasma half-life was 18.25 hours.

### High-dose sodium selenite stabilized more than a third of the patients with therapy-resistant, advanced tumors

The results regarding the anti-tumoral effect of sodium selenite were very promising, but must be further examined in additional studies due to the low number of patients. Sodium selenite displayed no uniform effect on the tumor size. However, after the sodium selenite treatment, 13 patients (38 %) showed a stable disease. 16 patients (47 %) were stable after subsequent chemotherapy. In the following six months, one patient showed a gradually improved response to the sodium selenite treatment. Half a year later, the tumor was no longer detectable. The patient is still alive and has been recurrence-free for more than six years.

In total, the sodium selenite treatment did not result in a significantly higher overall survival rate. This was primarily because of the small number of patients in the study. However, therapy with high-dose sodium selenite and subsequent chemotherapy also had no negative influence on survival. Two patients are still alive (after five years and one year). The median value of the survival period after sodium selenite treatment was 6.5 months; since the participants in the trial had therapy-resistant advanced tumors, this was a fairly long time.

Stable disease for 38 % of the participants after sodium selenite therapy, or for 47 % with a subsequent chemotherapy who showed a stable disease, is a significant indication for additional studies with high-dose sodium selenite as monotherapy.

### Sodium selenite reversed chemotherapy resistance

The SECAR study shows that high-dose sodium selenite by itself is able to affect certain tumors. Indeed, this effect can be intensified by subsequent chemotherapy. It is especially interesting to note that many of the patients responded again to their first-line chemotherapy. In these patients, the therapy with high-dose sodium selenite could reverse the previous chemotherapeutic resistance.

In the SECAR study, very high doses of sodium selenite were administered in 20 or 40 minutes. Since sodium selenite has a short half-life period, additional studies should examine whether a steady-state status can be attained with an infusion over a prolonged time period, resulting in an improved clinical effect of sodium selenite and changes in the maximum tolerated dosage.

## Plasma selenium concentration for high-dose sodium selenite therapy

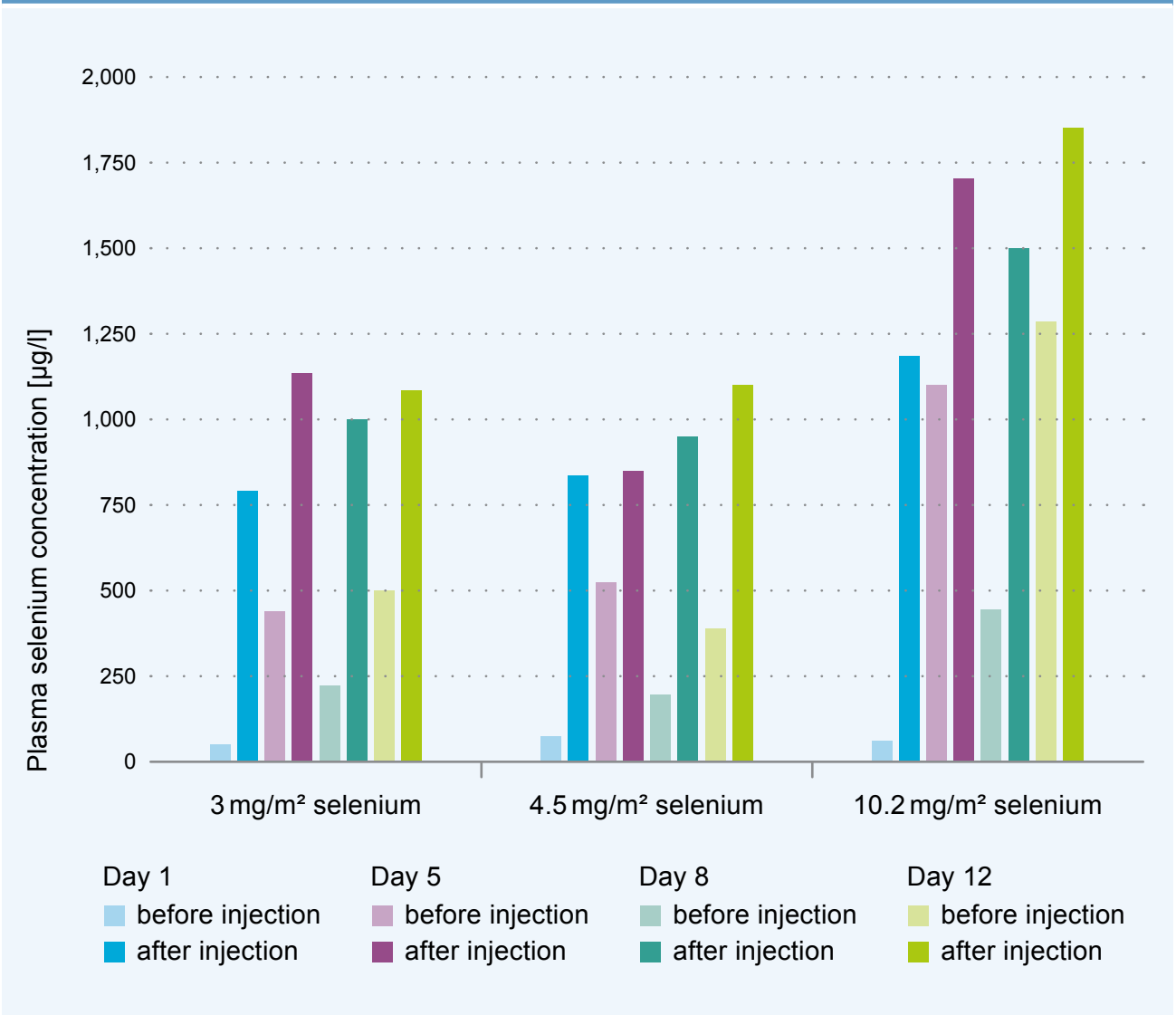


*Fig. 4*


[1] Brodin O, Eksborg S, Wallenberg M, Asker-Hagelberg C, Larsen EH, Mohlkert D, Lenneby-Helleday C, Jacobsson H, Linder S, Misra S, Björnstedt M
*Nutrients. 2015 Jun 19;7(6):4978-94. doi: 10.3390/nu7064978*
Pharmacokinetics and Toxicity of Sodium Selenite in the Treatment of Patients with Carcinoma in a Phase I Clinical Trial: The SECAR Study

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01 D01 756/A · medical experts · 03/16